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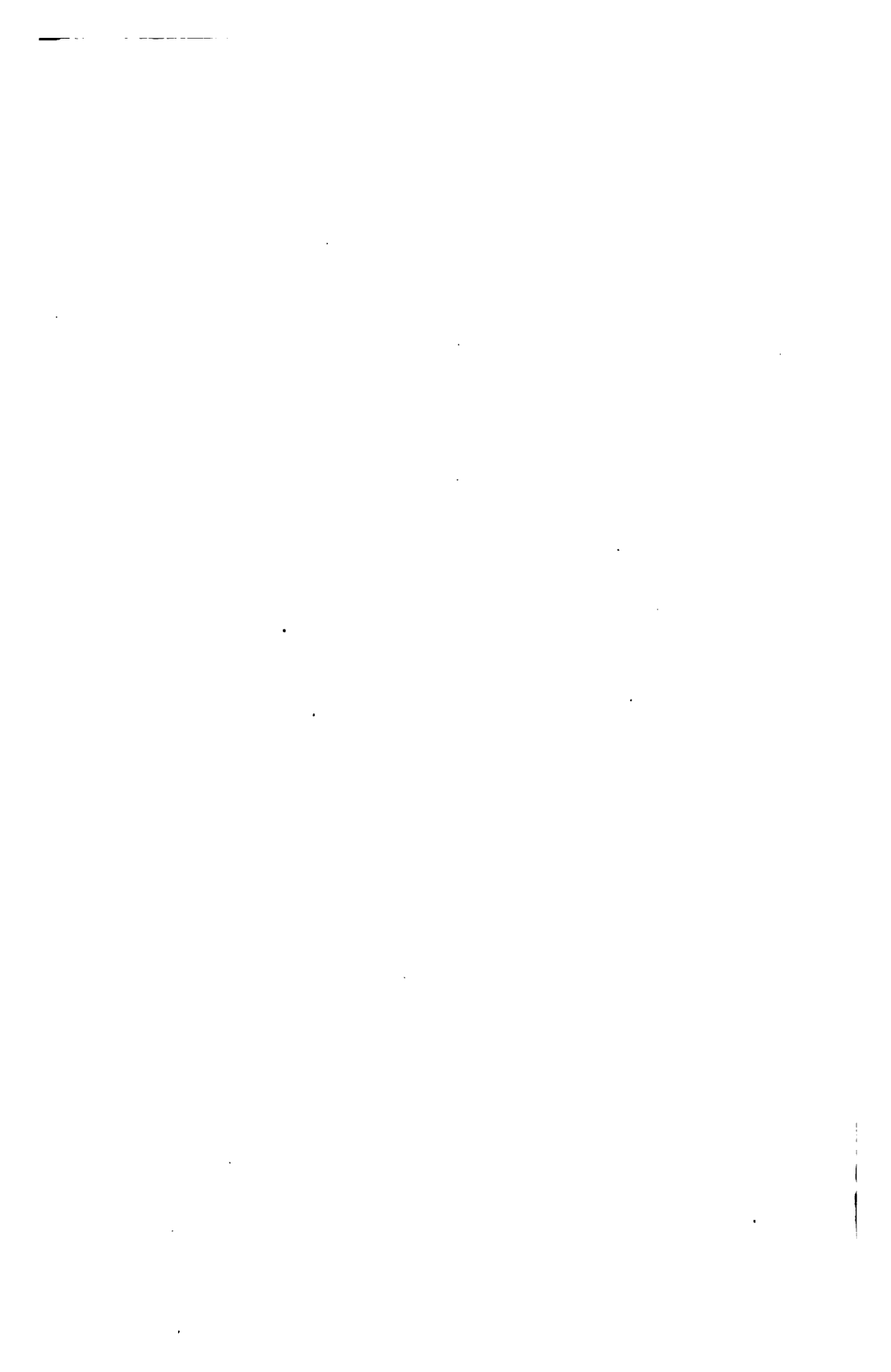
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ORIGINAL ARTICLES

**PERFORATION IN CANCER OF THE STOMACH.<sup>1</sup>**

BY JULIUS FRIEDENWALD, M.D.,

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AND

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WHILE perforation is a complication often noted in the course of gastric ulcer and reports on this condition abound in the literature, there are very few reports of a similar complication in the case of gastric cancer.

Brinton's statistics, which are frequently quoted, show 17 perforations into the peritoneum among 507 cases of cancer of the stomach. In this collection there is one case of gastric fistula due to perforation involving the anterior abdominal wall. In the American edition of Riegel's<sup>2</sup> *Diseases of the Stomach*, edited by Stockton, perforation into the abdomen is classed as a rare termination of cancer of the stomach. W. Hale White, in Allbutt's *System*, gives 4 per cent. as the frequency of the complication. Perry and Shaw<sup>3</sup> made a study of 306 fatal cases of cancer of the stomach collected between 1826 and 1900. There were 13 cases of perforation with acute peritonitis and 7 with localized abscess. Smithies<sup>4</sup> gives 2.5 to 6 per cent. as the frequency of perforation in

<sup>1</sup> Read at the meeting of the American Gastro-enterological Association, Atlantic City, May 6, 1918.

<sup>2</sup> Edited by Stockton, 1903, p. 698.

<sup>3</sup> Guy's Hospital Report, 1904.

<sup>4</sup> *Cancer of the Stomach*, 1916, p. 101.

gastric cancer. In our series<sup>1</sup> of 1000 cases of cancer of the stomach published in 1914 there were 23 (2.3 per cent.) presenting signs of perforation, but only in 3 of these cases was the perforation demonstrated.

Perforations of the stomach from any cause may be either acute or chronic. In the first-mentioned variety the perforation is accompanied by the urgent symptoms of a spreading peritonitis. With the chronic form there is time for the development of a reaction on the part of the peritoneum, and by organization of the exudated lymph adhesions, bind together adjacent viscera and endothelial surfaces, and so wall off the area of infection which occurs.

The dearth of reports on perforated gastric cancer may be explained by the fact that an acute perforation is not often observed and that the hopeless outlook for cure of the cancer distracts attention from the complication when chronic perforation has occurred.

The spread of gastric cancer from its original situation is by way of the lymphatics. Permeating the lymphatics of the gastric wall the malignant epithelial cells reach the subperitoneal group and stimulate the connective-tissue reaction in their vicinity, with resulting adhesions between the tumor and surrounding viscera or the abdominal wall. The tumor cells then enter the extragastric lymph spaces and metastasis to glands and distant organs occur. The progress of the epithelial cells through the permeated lymphatics is always followed by a fibrosis of the area involved. Wilensky and Thalheimer show that the ulceration in cancer of the stomach is certainly associated with if not caused by necrosis, and the digestive action of the gastric juice. The process is a slow one and will allow sufficient time for a considerable development of the adhesive and fibrous reaction just described. This barrier thickens as the ulceration approaches the peritoneal coat and so builds up a resistant wall against the extension of the process. When perforation does occur the opening is made into a protected cavity and a chronic abscess results. As shown by White, in the case of ulcer such perforations may be revealed by roentgen-ray examination. In our experience chronic perforation of cancer of the stomach indicates an inoperable lesion. Four cases, three acute and one of chronic perforation, have come under our observation.

CASE I.—*Acute perforation of carcinoma of the stomach.* On August 3, 1908, Mrs. T. S., aged sixty-two years, sought advice for indigestion which had been annoying her for three months. She had never had indigestion before and dated her gastric disturbance to an upset following a dietary indiscretion in partaking too freely of sausage. Since then her digestion had been poor, notwithstanding the greatest care in her diet. The patient has lost twenty pounds in

<sup>1</sup> Friedenwald: A Clinical Study of One Thousand Cases of Cancer of the Stomach, AM. JOUR. MED. SC., November, 1914.

flesh and complained of loss of appetite, pressure and abdominal distention, nausea, occasional vomiting and gastric pain not in any way related to food. The vomited material was light in color and far in excess of the last meal partaken.

On physical examination the heart and lungs were found normal. The abdomen was much distended and peristaltic waves could easily be made out. A hard mass was readily palpated, which was situated at about the center of the epigastrium, and which was about 4 cm. long and 6 cm. in breadth. The inguinal glands were markedly enlarged. The test-meal revealed an absence of free HCl, presence of lactic acid and evidence of marked retention. The diagnosis of carcinoma at the pylorus, with obstruction, was made and operation advised.

At the operation a large carcinomatous mass was found involving the pylorus and nearly half of the body of the stomach; on account of metastases in the mesenteric glands, as well as in the liver, no attempt was made at excision. A gastro-enterostomy was performed. The patient made a satisfactory recovery from the operation and was able to take nourishment better for a time. The emaciation, however, progressed, and after two months, following operation, the patient became melancholic and developed suicidal tendencies, requiring the constant care of a trained attendant. Suddenly, on the morning of December 10, 1908, she was seized with an intense abdominal pain, which was followed by symptoms of intense shock, a rapid pulse, clammy extremities and cold perspiration. Three-quarters of a grain of morphin was required within an hour for the relief of the pain. The patient died within a few hours. A partial autopsy was performed and a large perforation was observed in the midst of the carcinomatous mass at the pylorus. The gastro-enterostomy opening was patent.

CASE II.—*Acute perforation of carcinoma of the stomach.* J. S., aged fifty-seven years, male, consulted us on January 20, 1910, for a digestive upset, with which he had been troubled for six months. He complained of pain in the region of the stomach, nausea, indigestion, weakness and loss of thirty-six pounds of flesh.

He was found to be a very emaciated individual, with a large mass in his abdomen in the region of the stomach. The gastric contents presented an absence of free HCl and contained lactic acid and Oppler-Boas bacilli. The diagnosis of carcinoma was made without question. Two days following the examination the patient was suddenly seized with intense abdominal pain, which lasted several hours and which was only slightly relieved by hypodermic injections of morphin.

The patient died within six hours, and on section an opening sufficiently large to admit a lead-pencil was observed in a carcinomatous mass in the body of the stomach. The abdominal cavity was filled with gastric contents.

CASE III.—*Chronic perforation; fistulous opening through the abdominal wall.* William F., colored, aged fifty-three years, entered the Mercy Hospital on December 6, 1913, and died on December 9, 1913.

The patient has been troubled with indigestion for the past three months; he had nausea and vomiting during this time and suffered from distention and fullness after food. He noted a swelling in the epigastrium; considerable shortness of breath; loss of strength and flesh. The patient had occasional chills, followed by a moderate rise in temperature. There was no history of hematemesis or jaundice, though the stools were frequently tar-colored. There was a history of the use of intoxicants and tobacco to excess.

On physical examination the patient was found to be a very feeble and markedly emaciated negro; the heart and lungs were normal. The abdomen was soft and a definite mass was noticed on the right side just below the costal margin, which was easily palpable, the size of a hen's egg, and which was somewhat nodulated. The inguinal and axillary glands were much enlarged and easily palpable.

Just to the left of the median line and above the umbilicus a scar of an operation was observed, situated at the lower angle of the scar was an ulcerated area, in the center of which was found a fistulous opening, connected with the interior of the stomach through a sinus. Milk taken by the mouth discharges in a curdled state in about an hour after ingestion upon the external abdominal wall. The margin of the sinus was stony hard on palpation. A more careful history could not be obtained, nor could a very satisfactory examination be made on account of the great weakness of the patient. A diagnosis of carcinoma with perforation and fistulous sinus was made. The patient died in three days from exhaustion.

At the autopsy a carcinoma of the pylorus was found with metastases in the liver, kidneys and bronchial glands. The sinus extended from the interior of the stomach through the cancerous mass to the external abdominal wall, where it opened just above and slightly to the left of the umbilicus. The fistulous tract consisted of ulcerated carcinomatous tissue, and through it the gastric contents were discharged.

CASE IV.—*Acute perforation of cancer of the stomach.* G. E. W., white, aged seventy-three years, was admitted to the Mercy Hospital, March 29, 1916, on account of severe abdominal pain. The onset of his symptoms occurred at noon, when his trouble was diagnosed acute indigestion. Morphin given at this time did not relieve the pain. Two hours later he came to the hospital and the great pain, tenderness and rigidity of the abdomen led to an immediate diagnosis of perforative peritonitis. There was no vomiting, but persistent nausea. The general condition of the patient was bad; he was cyanotic, with a rapid pulse and showing every sign of great distress. There was dulness in both flanks. A ruptured cancer of



the stomach was considered the cause of the peritonitis, because of the history of a six months' period of indigestion and a loss of twenty-five pounds in weight during this period. Operation was advised and accepted.

*Operation* March 29, 1916, 3 P.M. Anesthesia: novocain and ether. Right rectus incision with transverse cut at upper angle; gelatinous fluid in peritoneal cavity. The perforation, about one-sixteenth inch in diameter, was found in a small annular cancer near the pylorus. Apparently the omentum had been loosely adherent to the opening. The opening was burned with the cautery and the area turned in with mattress sutures. The omentum was sutured over this region. Drains were carried to the region of the perforation and the right kidney fossa. The pelvis was drained through a suprapubic wound. The patient rallied from the anesthesia, but died about thirty-six hours after the operation. Postmortem examination was not permitted.

### PROGNOSIS IN HEART DISEASE IN RELATION TO AURICULAR FIBRILLATION AND ALTERNATION OF THE PULSE.

BY PAUL D. WHITE, M.D.,

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IN the course of an investigation three years ago (1914) on the frequency of alternation of the pulse, interesting groups of cases were accumulated and studied with the polygraph and electrocardiograph. Three series of cardiac patients, comprising 100 each, were collected with relation to the type of pulse and cardiac rhythm shown. The first series was composed of cases with auricular fibrillation, the second of cases with alternation of the pulse and the third of cases with normal cardiac rhythm without alternation. Heart-block, auricular flutter and paroxysmal tachycardia were not included *per se*.

For study as to prognosis the groups of auricular fibrillation and pulsus alternans were subdivided, each into three classes. The patients with auricular fibrillation were subdivided into (a) those who showed aberrant ventricular complexes, the so-called "bundle branch block," (b) those who showed ectopic ventricular contractions and (c) those who had uncomplicated auricular fibrillation. Since some of these 100 cases had not been electrocardiographed they could not all be so grouped. The patients with alternation of the pulse were also subdivided as already reported in an earlier paper<sup>1</sup> into (a) those who had constant pulsus alternans, (b) those

<sup>1</sup> White, P. D.: AM. JOUR. MED. SC., July, 1915.

having marked alternation after premature contractions only and (c) those showing only slight alternation after premature contractions. It was believed that the greater the grade of alternation the worse the prognosis. All of the 100 patients with pulsus alternans had radial pulse tracings taken. The 100 patients with normal rhythm, also studied cardiographically, were not subdivided.

At the present time, just three years after beginning to collect these series of cases and two years after finding the most recent case, I have looked up the patients in order to determine their present condition. The results of this investigation I have tabulated (see Table) and am reporting here briefly for what they are worth. About one-third of the patients have been lost sight of, but the results from the others are of interest and of value.

Condition.	Type.	Total.	Cases followed until present time.	Better.	Unchanged.	Worse.	Dead.	Per cent. dead of cases traced.
Alteration of the pulse	Constant	26	22	2	0	0	20	91.0
	Marked after premature beats	16	12	0	0	0	12	100.0
	Slight after premature beats	58	42	4	13	1	24	57.0
	Total of alternation	100	76	6	13	1	56	74.0
Auricular fibrillation	Cases electrocardiographed	69						
	(1) Aberrant ventricular complexes	5	4	0	0	0	4	100.0
	(2) With ectopic beats	11	7	1	1	0	5	71.0
	(3) Uncomplicated	53	35	2	18	4	11	31.0
	Cases not electrocardiographed	31	16	2	3	1	10	62.5
	Total of auricular fibrillation	100	62	5	22	5	30	48.0
Normal rhythm	No alternation, fibrillation, paroxysmal tachycardia, flutter or heart block	100	49	8	15	3	23	47.0

**DISCUSSION.** From a glance at the Table it is obvious that in these series pulsus alternans taken *in toto* give a much poorer prognosis than auricular fibrillation, but that auricular fibrillation as such adds little if anything to the gravity of prognosis in a case of heart disease. The higher grades of pulsus alternans are almost twice as grave as the slight degrees, *i. e.*, slight alternation following premature contractions, while between the two severe grades, constant alternation and marked alternation after premature contractions, there is little to choose, the mortality in such grades together being almost 100 per cent. (94 per cent.) within a period of three years. However, even the cases with slight alternation after premature beats have a mortality of over 50 per cent. within

the three years and definitely higher than either the auricular fibrillation or the normal rhythm averages.

In the case of auricular fibrillation I have often wished that I might be able to pick out by graphic methods the more serious cases, as one can do in pulsus alternans, as I have shown above. By examining the Table one sees some clues which help one in this attempt. For this selection electrocardiograms are necessary. Patients who show auricular fibrillation complicated by aberrant ventricular complexes or by ectopic ventricular contractions have a much graver prognosis than the uncomplicated auricular fibrillation, much more than twice as grave, especially in the case of the aberrant ventricular complexes, where in my small group of cases the mortality was 100 per cent. within three years. Such a finding might be expected because the electrocardiograms indicate serious myocardial damage or irritability in the ventricles. Such diseased or hyperirritable ventricular muscle does not stand up under the strain of auricular fibrillation the way relatively healthy ventricular muscle does. It is probable that one may regard these two conditions complicating auricular fibrillation as important as the presence of pulsus alternans in the case of a non-fibrillating heart. In fact, one of the patients tabulated above as having aberrant ventricular complexes and auricular fibrillation combined had been seen by me before his heart became arrhythmic and a radial pulse tracing at that time showed pulsus alternans.

Further confirmation of these findings in larger groups of cases would be of interest. The prognostic value of electrocardiograms as well as of radial pulse tracings is brought out by this investigation, the former especially as regards auricular fibrillation and the latter as regards alternation of the pulse.

**SUMMARY.** 1. Three groups of 100 patients each, showing (1) pulsus alternans, (2) auricular fibrillation and (3) normal rhythm, have been studied with relation particularly to prognosis. A large number of each group has been followed for two or three years and the condition determined at the end of that time.

2. Seventy-four per cent. of the cases with pulsus alternans, 48 per cent. of the cases with auricular fibrillation and 47 per cent. of the cases with normal rhythm have died.

3. The higher grades of alternation of the pulse carry with them an especially high mortality, nearly 100 per cent. within three years.

4. The cases with auricular fibrillation complicated by aberrant ventricular complexes seem to be very fatal (100 per cent. in the present series), those cases with ectopic ventricular contractions complicating the fibrillation have a mortality almost as high as the total of alternation while uncomplicated auricular fibrillation has a surprisingly low mortality percentage.

I wish to thank all those who have helped me to follow the cases discussed in this paper, especially Miss Catharine Thacher for her painstaking work.

## A MODERN ASPECT OF THE TREATMENT OF ULCUS VENTRICULI.

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*A. Prophylaxis.* In the prevention of ulcer of the stomach, universal rules, as in certain contagious diseases, cannot be laid down because no one factor can be held responsible for the occurrence of the ulcer. In this disease prophylaxis begins at a time when the patient presents himself with gastric symptoms, indicating the existence of hypersecretion or hyperacidity, and in some cases predominating motility disturbances. When such symptoms are allowed to persist, ulcer of the stomach may develop.

Our first duty is to determine the etiological factors of his complaint, and from a clinical standpoint the following points must be taken into consideration:

1. Status of the individual.

- (a) Sthenic.

- (b) Asthenic.

2. Local intra-abdominal diseases, like chronic appendicitis, cholelithiasis, obstipation.

3. Focal infections.

1. *Status.* As to the sthenic type (status apoplecticus) it is not an uncommon experience to have well-preserved, healthy looking individuals (mostly men) complain of pyrosis, and even moderate pains two or three hours after a meal, of fulness relieved by belching. These symptoms are aggravated by hurried eating, especially if quality or quantity of food is disregarded. These people are particularly troubled because previously they had enjoyed unusual privileges on the part of the gastro-intestinal tract. They ate at all hours, gulping down a heavy lunch and hurrying back to perform hard duties of a mental and physical sort. Suddenly they begin to notice that mental and physical rest, moderate observation of diet and restraint in the use of heavy cigars become necessary to their well-being.

Such a symptom-complex may indicate the real pre-ulcerative stage, and it is our duty not to look lightly upon the complaints. The patient must be told that the functions of his stomach have exceeded the point of accommodation to abuses, and from now on his mode of life must be regulated in order to prevent the formation of an ulcer in the stomach. The symptoms are to be controlled by a non-irritating, easily digested diet, allowing only milk, eggs, thin cereals, toast and butter for four or five days, gradually adding

vegetables in purée form, boiled chicken, lamb chops, veal, ham and cooked fruits. His future mode of life must be mapped out.

In our experience such individuals are much benefited by two substantial meals taken at home morning and evening. During the lunch-hour crackers and milk, or tea with milk, or zoölak, not very cold, and zweiback should suffice to satisfy hunger.

The breakfast should consist of orange juice or grapefruit, or baked apples with cream, or stewed peaches with cream, eggs in any form (except hard boiled), cereals, bread and butter, and weak coffee, cocoa, tea or milk.

The evening meal may include the following:

Grapefruit, oysters, vegetable, noodle or barley soup, not spiced, fish plainly cooked or fried in butter.

Meats: Lamb, steak (well done), roast beef, chicken, veal, cooked ham, or white of turkey.

Vegetables: Fresh green vegetables cooked, salads, potatoes, stewed fruit.

Light puddings, cream cheese and Vichy water. We must not allow spicy substances, nor duck, goose, canned goods, coarse vegetables, excess of sweets or ice-cold drinks.

From the hygienic standpoint the patient must be told to eat slowly and at regular intervals, taking a short rest after the evening meal, and to smoke moderately. He should utilize his week-ends for complete relaxation and spend the summer vacation at a spa (Saratoga, etc.).

*Asthenic Type.* In contradistinction to the type just described, when the ulcer is the outcome of continuous local irritation, there is the asthenic type (habitus Stiller), in which physical inferiority predisposes to ulcer. Here, while fulness and distress after meals and sour eructation are of a frequent and troublesome nature, the more or less indefinite and negligible objective findings outside of the status and hyperacidity cause the physician to look lightly upon the complaint. Overfeeding, with indifference as to quality on the one hand, or extreme care, resulting in still greater loss of weight as well as the existing vagotonia, finally lead to ulcer. This group may also include the chlorotic girl, with tendency to ulcer, partially because of the anemia and probably because of her perversion in the selection of sour, spicy food as well as chalk.

The method of preventive treatment depends on the general condition of the patient. If not very much run down we first restrict fluids, allowing food in semisolid form of a non-irritating character, in smaller quantities and at more frequent intervals. The dietetic regime may be laid out as follows:

Breakfast. Cereals cooked in milk in a double boiler, prepared thick and taken with butter; 1 to 2 eggs, soft boiled or scrambled; toast with butter; 150 gr. of cocoa or milk or tea with milk. At 10 A.M. a cup of warm milk.

Noon. Chopped or minced meats boiled or fried in butter (chicken, pigeons, veal, lamb); fresh green vegetables cooked and in purée form (spinach, carrots, asparagus tips, cauliflower, green peas, string beans, turnips); light pudding, apple-sauce and toast. At 4 P.M. a cup of warm milk.

7 P.M. Same as breakfast, including a baked apple and cream cheese. Before retiring, another cup of warm milk.

For patients who are very much run down a modified Weir Mitchell rest cure should be insisted upon from the start. The modification consists in not using a milk diet exclusively for the four to six weeks of treatment and not an absolute confinement to bed for longer than three or four days. Furthermore, the four to six weeks of treatment should serve as an education to the patient in taking care of his digestive organs in particular and mode of living in general.

During the first three or four days, while in bed, 6 ounces of warm milk and 2 ounces of sweet cream are given every two hours from 8 A.M. to 10 P.M. When there is aversion to the excessive intake of milk we add to the milk at every second or third feeding weak tea or caffein-free coffee. Should there be a tendency to diarrhea, strained barley, rice water or cocoa may be added to the milk.

During these days a cold rub in the morning and a light massage mornings and evenings are very helpful. When bloating or tendency to constipation exists a soapsuds enema before retiring is ordered.

After four days the intervals of feeding are increased to three hours, and to every second meal we add one or two soft-boiled eggs and a thin cereal. This is continued to the end of the week, during which time the patient is allowed to walk intermittently two or three hours in the course of the day. If the symptoms have receded a more liberal diet is allowed, *i. e.*, toast and butter, mashed potatoes and at about the end of the second week the diet outlined for milder cases can be tolerated.

Patients are benefited by wearing well-fitting abdominal binders, which not only raise up the abdominal viscera but assist the tone of the abdominal wall, thereby increasing the tone of the stomach. General hygienic measures, like appropriate hydrotherapeutics and moderate exercise, must constitute an important part of the treatment. A few suggestions as to specific hydrotherapeutics may be in place. When still in a weak and helpless state cool packs, either of the entire body or of three-quarters of the body, are very beneficial, with warmth applied to the feet and cold to the head. The patient remains in the pack for one hour. The method can easily be taught to a member of the patient's family.

A thoroughly wrung-out sheet, in water of a temperature of 70° to 80° F., is spread out on a blanket, the patient is quickly wrapped in the wet sheet from neck to feet, or knees, and over this the flannel blanket is tightly wrapped.

When the patient begins to feel stronger a half-bath is ordered, at a temperature of 95°, decreasing daily until 75° to 80° is reached. He is kept in the bath for from five to ten minutes, constantly rubbing the chest. A cold towel is applied to the head. Before leaving the bath, water of 5° lower than the bath is poured over the spine. The body is quickly dried and the patient is made to rest for at least half an hour. Later on a morning shower, first of tepid and gradually cold temperature, is to be employed. A Priesnitz compress over the abdomen, to be kept overnight, is very beneficial.

The morning hydrotherapeutic measures should be carried out either on an empty stomach or half an hour after a cup of warm milk. As to drugs it is often unnecessary to use any at all. The absence of drugs is often an excellent suggestive therapeutic with an intelligent patient. It makes him feel that the disease is not serious.

When the above treatment alone does not relieve the symptoms of hyperacidity alkalies (magnes. usta and natrii bicarbon.,  $\text{ãã}$  1.0 t. d.) or, if diarrhea is annoying, bismut. subcarbon., 1.0 t. d. is very useful. Because the hyperacidity in these cases is a part of the vagotonia, atropin sulphate, 0.0005, or extr. belladon., 0.02 in the form of suppositories, 2 t. d., should be given.

The nervous symptoms which are often annoying during the first or second week of the treatment, notwithstanding hydrotherapeutic procedure, may call for nerve sedatives. Bromides are usually depressing when given for a greater length of time, and may even aggravate the gastro-intestinal symptoms. Much more useful are the valerian preparations. The objection to most valerianates lies in the taste and odor. The proprietary ones, like borneval, valedol, etc., are very expensive. We found that a cold infusion served the purpose very well. It is made as follows: One teaspoonful of dried valerian roots is put into 8 ounces of hot water and allowed to stand all day. At night it is passed through a piece of gauze and taken cold with sugar. The constipation in these cases should be overcome by diet, going to stool at a regular time and, if necessary, a daily soapsuds or saline enemas.

We have endeavored to outline more or less in detail the methods of treatment in both sthenic and asthenic individuals, the application of which can result in prevention of ulcer formation. From the standpoint of prognosis it is important to point out that a sthenic individual once having shown gastric symptoms must be cautioned against indiscretions in diet for the rest of his life. With the asthenic individual (in whom the local gastric symptoms are more the result of systemic inferiority), if treatment has resulted in considerable gain in weight and a toning up of the system in general and the gastro-intestinal tract in particular the benefit may persist through the rest of his life, without any more dietetic or hygienic restrictions than the average healthy person needs.

The asthenic individual, by virtue of the above treatment, is

transformed into a person who can adapt himself to his duties and external influences, although the inborn stigmata of his habitus persist.

*2. Local Intra-abdominal Diseases.* The etiological relation of chronic appendicitis, and more rarely cholelithiasis to formation of an ulcer in the stomach, was pathologically demonstrated conclusively by Roessle, Lichtenbelt and surgically by Moynihan, Mayo and others. Some observers, among them Rosenow, hold that the mode of production of ulcer secondary to chronic appendicitis or cholelithiasis is that of infection. Roessle, von Bergman and Lichtenbelt, on the other hand, believe that sympathetic nervous irritation causes secretory and motor disturbances in the gastric mucosa, leading to local ischemia, erosion and ulcer formation.

We are of the opinion that an ulcer in the stomach is, as a rule, not the result of infection. Bacterial infection causes inflammatory changes which have different characteristics from those of the ulcer. The round peptic ulcer, with its punched-out appearance and overhanging edges, impresses one definitely that chemical, thermic or traumatic agents are the existing factors, and the primary cause is to be looked for.

In chronic appendicitis as a primary cause the conception of Roessle and Lichtenbelt is the more plausible. The clinical manifestations point to the correctness of such a conception. The local gastric symptoms, even before the ulcer exists, indicate so strongly an ulcer in the stomach that a mistake is often unavoidable.

Such pre-ulcerative symptoms in connection with chronic appendicitis can certainly not be attributed to bacterial infection. Surgical findings in cases of chronic appendicitis, or even gall-bladder trouble where the symptoms point to gastric ulcer, show in the vast number of cases an atrophied, small or obliterated appendix, sometimes containing fecoliths or other foreign bodies.

Extensive adhesions around the appendix or gall-bladder, or both, give rise to a gastric symptom-complex entirely different from ulcer. The pains are of a more continuous nature, with sensation of abdominal distention; gastric or intestinal stagnation as a result of kinks; or an open pylorus with rapid emptying because the adhesions interfere with the normal contractions of the pylorus.

Gall-bladder affections giving rise to gastric symptoms simulating ulcer and finally leading to ulcer formation also prove upon removal to be small, contracted and atrophic, with a greatly destroyed mucous membrane.

Chronic functional constipation, causing prolonged gastric hyperacidity, may finally lead to formation of ulcer.

From what has been said it seems to us plausible to assume that gastric disturbance manifesting itself clinically as hyperacidity, if reflex to a disease of intra-abdominal organs (appendix, gall-bladder, colitis or rectal or colonic constipation), the primary seat of the



affection in the organs named is mostly in the mucosa, with atrophic changes of greater or lesser degree. If the organs, on the other hand, show changes in the serosa leading to extensive adhesions the gastric symptoms are those of motility disturbance. The first class gives clinically the symptom-complex closely simulating ulcer, such as periodicity, relation of pain to quality, quantity and time of food taken, digestive hypersecretion and hyperacidity and good appetite. In the second class the gastric symptoms are pressure and distress after meals, sometimes pain, only relieved by vomiting, poor appetite, coated tongue, bad taste and sallow countenance.

The fact that the atrophic diseases of the organs named lead to gastric hyperacidity and ulcer seems to us a further proof that the bacterial invasion cannot be the primary factor in ulcer formation, but the pathological interrelation lies, as pointed out above and described by us elsewhere, in the nervous mechanism.

The foregoing discussion may be of assistance in the prophylaxis of ulcer in the stomach. In cases of hyperacidity, when the clinical diagnosis points to an appendix or gall-bladder, the removal of the diseased organs leads, in a great majority of cases, to a complete cure and prevents the formation of an ulcer.

Functional constipation causing hyperacidity must be treated appropriately in order to prevent ulcer formation. Dietetic regime is the most valuable item in the treatment. The food should be non-irritating but still bulky. Cereals well prepared (excluding rice and barley); vegetables in puréeform partaken of in large quantities; fats in the form of cream, butter and olive oil, 1 tablespoonful 3 t. d. before meals, are very efficacious. Meats should be taken in small quantities, not fried or seasoned, so as not to excite excessive secretion. Fruits like baked apples or apple-sauce or fruit jellies, later peeled ripe apples, cherries, pears, plums are allowed. Because of the tendency to gastric irritation and the predominance of the descending type (spastic) of constipation it is best to avoid eating berries, because of the seeds they contain, until the gastric symptoms and objective signs of spastic constipation disappear.

As to medication, belladonna is doubly valuable, because it serves as an antacid and antispasmodic. It may be given either in powder form, as the extract, 0.01, 3 t. d., one-half hour after meals, or in suppositories, 0.02, 2 t. d. Olive oil enemata, 8 ounces, to be retained overnight, for one week every night and then every other night to the end of one month, and then once a week for another month, and finally an oil enema at night when one or two previous days show constipated movements. The evacuation of the oil, even with a satisfactory movement, should be followed by a small soapsuds or saline enema, in order to wash away the oil from the colon, thereby avoiding the irritation that may result from the fatty acids formed. Some patients are irritated by the pure oil; to avoid this the oil can be prepared with a teaspoonful of sodium bicarbonate in the form of an emulsion.

The treatment outlined, if conscientiously carried out, brings about gratifying results, so that the symptoms of hyperacidity and constipation may disappear forever. The patient is advised that the first recurrence of the symptoms will necessitate a repetition of the treatment.

The direct influence of massage on constipation, by furthering the fecal contents toward the sigmoid and rectum, has been shown by means of roentgen rays to be fallacious. Nevertheless, massage in the atonic type of constipation has a beneficial effect by raising the tone of the abdominal and intestinal musculature.

3. *Focal Infection.* As to prevention of ulcer of the stomach by the removal of focal infections, like pyorrhea alveolaris and tonsillar and prostatic infections, the undertaking is more difficult. We have already stated that our clinical conviction does not permit us fully to accept the infection theory of ulcer of the stomach. It is, however, plausible that once an ulcer is formed the healing is prevented by an infection. This might explain the seasonal exacerbation of symptoms in ulcer corresponding to the time of the year when tonsillitis is prevalent.

As a word of caution it must be emphasized that before radical measures are taken to treat the local infection—be it teeth, tonsils or prostata, we should have a positive diagnosis established by competent specialists—the bacteriologist, roentgenologist and clinician.

*Internal Treatment of Ulcus Ventriculi.* Since the inception of the extremely strict treatment of ulcus ventriculi as advocated by von Leube and Ziemssen, modifications have been abundant. There has hardly been a gastro-enterologist of importance who in the course of his career did not find that a modification of the original Leube treatment would be beneficial. Thus have originated useful methods, like the Bourget, Sippy, Einhorn-duodenal feeding, Lenz and Smithies, to be described in full. A great number of other modifications that have unfortunately flooded medical literature are not based on any scientific principle and shall not be mentioned. The modifications mentioned above, advocated and successfully carried out by experienced authorities, demonstrate to us that after all individualization, guided by proper judgment, is the only rational method.

In describing their respective methods the authors have aimed to meet the existing functional disturbances of the stomach and thereby give the ulcer a chance to heal. So have the older clinicians, von Leube, Ziemssen, Ewald, Einhorn and Boas, advocated complete rest to the stomach, which in turn would subdue secretions and acidity and stop hemorrhages if present.

Bourget, Fleiner, Sippy and J. Kauffman have chiefly aimed at neutralization of existing acidity as a most important factor in bringing about a cure.

These principles hold good in the typical cases when an ulcer in

the florid stage gives rise to either hemorrhage, excessive secretion and acidity, increased peristalsis or pylorospasm and accompanying pain. In describing the various methods of treatment we shall give our reasons why one or another method is preferable.

The more advanced diagnostic methods have taught us, however, that ulcer of the stomach exists in a fair number of cases when the above symptoms are not outspoken. In order to treat such cases successfully it is necessary to know the causative factors of the existing symptoms, and we advise the following guide:

1. Is it a bleeding ulcer (occult, profuse)?

2. Are pains, hyperacidity and hypersecretion the main existing disturbances?

3. Is the patient entirely free between attacks, so that even mental, physical and dietary excesses have no influence? or must he always be very careful, and if so, why?

4. Is the ulcer coexistent with subacidity or anacidity?

1. *Bleeding Ulcer.* A. Occult. The frequency of occurrence of occult blood in ulcus ventriculi is estimated by Boas, Kuttner and others to be much higher than that in the Mayo Clinic. Statistics have only relative value, inasmuch as the material in a surgical clinic, with predominating callous ulcers, would show a smaller number of cases with occult blood.

It is agreed, however, that the frequent demonstration of occult blood in the stool, excluding all sources of error, indicates that the ulcer is in a progressive state, and treatment almost as strict as that for profuse hemorrhage should be carried out. It is important to know that the persistence of occult blood, notwithstanding exact treatment for a few weeks, causes suspicion that malignancy exists and justifies exploratory operation.

The dietetic treatment for both occult and profuse hemorrhage will be considered together. Management of a case in the course of profuse hemorrhage needs special consideration.

B. Profuse Hemorrhage. The intensity of the treatment will depend on the severity and the effect of the bleeding. The patient should be put to bed, flat on his back and the legs of his bed elevated; an ice-bag or an ice-water coil to the abdomen and a hypodermic injection of morphin (0.005) in order to allay anxiety.

Nothing should be allowed by mouth. The thirst and dryness in the mouth should be overcome by giving the patient small pieces of ice, but allowing him to swallow very little of it. Per rectum, by way of the Murphy drop method, one pint of a Ringer solution can be given twice daily. In many cases this course of treatment alone for two or three days suffices to bring the hemorrhage to a standstill. In very weak individuals it may be necessary to give 1 pint of a 18 to 20 per cent. glucose solution per rectum on the second or third day. When the symptoms due to hemorrhage are more alarming one should immediately resort to more stringent methods.

The so-called autotransfusion, which consists in bandaging the upper and lower extremities to obstruct the venous flow but not obliterate the pulse, is very useful. The intravenous injection of 5 c.c. of a concentrated sodium chloride solution is next in importance. If further means are necessary 20 to 50 c.c. of human serum intramuscularly is to be given. Coagulose, sterilized gelatin (20 c.c.) with or without calcium intramuscularly, or per os decoction of gelatin (15 in 150), 15 grams every two hours, emetin (0.015) intramuscularly and pituitrin, 10 to 15 drops intravenously, as well as thromboplastin, can be resorted to if necessary. Adrenalin should be given if the blood-pressure is very low. Essau in Germany and Mansfield in Nebraska advocate powdered alum in glycerin (10 in 100), 1 teaspoonful every two or three hours.

Stimulation is, as a rule, unnecessary, but if indicated, camphor intramuscularly may be employed. If the bleeding is profuse, so that an immediate replacement of fluid is of vital importance, hypodermoclysis of normal saline solution or the intravenous use of the same solution is to be employed. Still better is blood transfusion, because it serves as a hemostatic and at the same time stimulates the blood-making organs.

Fleiner advises gastric lavage with ice water, Ewald with hot water and Bourget with 1 per cent. liquor ferri sesquichloride solution. Lavage, as a rule, is dangerous and but seldom indicated. In some cases, when there is nausea and frequent emesis of blood-clots, no treatment is as good as lavage, with either of the above solutions, in order to wash away the clots and give the stomach a chance to contract.

Occult bleeding needs no active hemostatic measures, as a rule; in certain cases, however, long-continued occult bleeding leads to secondary anemia of such a degree that healing of the ulcer is prevented until blood transfusion and use of sodium cacodylate (0.05 to 0.1) intramuscularly, daily for a month, is employed.

If profuse hematemesis recurs within a comparatively short time, surgical intervention is indicated after the hemorrhage has stopped and the patient is in a fit condition. As a rule, however, gastric hemorrhages due to ulcer yield to medical treatment. Only rarely does it become necessary to resort to surgical intervention because of inability to stop the bleeding.

*Dietetic Regime with Bleeding Ulcer.* Feeding by mouth can begin the second or third day when there is occult bleeding, in profuse bleeding a day after hematemesis has ceased and there is no nausea or vomiting. It is important to note that we must be guided at the beginning of feeding by mouth by the sensation of the patient. In marked hyperacidity and hypersecretion, notwithstanding the existence of the occult blood, the pyrosis and the hunger pain make it necessary not to discontinue feeding by mouth at all.

In active bleeding the acidity symptoms disappear or diminish

because of the neutralizing effect of the free blood on gastric secretion. Here, too, the return to feeding by mouth is governed by the sensations (pyrosis and hunger pain) of the patient. The first day when feeding by mouth is begun 2 tablespoonfuls of ice-cold certified milk is given every hour from 7 A.M. to 10 P.M., and during the night in the case the patient awakes. If this is tolerated the quantity is doubled the following day and tripled on the third day. Experience teaches that patients who otherwise had an aversion to milk welcome it and bear it well after gastric bleeding. In milk the patient has a bland, easily digested and non-irritating form of all the three articles of food, in addition to that the necessary fluids, hemostatic calcium and other salts. During this time 1 pint of 10 to 20 per cent. glucose solution can be administered by rectum in the morning after the bowels are cleansed by a soapsuds enema and 1 to 2 pints normal saline by the drip method.

Hamburger prefers the use of plain lukewarm water per rectum, claiming that additions like glucose or salt may reflexly irritate the stomach. We see no reason for this overanxiety, our experience justifying the belief that a physiological salt solution or a glucose solution is absorbed better and is much less apt to cause irritation of the colon than plain water.

During these three days the ice-bag can be removed and a Priesnitz compress substituted, to be changed every twelve hours. On the fourth and fifth days we allow 200 gm. lukewarm milk every two hours from 6 A.M. to 10 P.M.; to every second feeding 2 tablespoonfuls of sweet cream are added to the milk. If the patient has no complaints we extend the intervals of feeding to three hours, 200 gm. of lukewarm milk and 50 gm. of sweet cream, and every second feeding add two soft-boiled eggs. This is given for the sixth and seventh day.

If there is no gastric discomfort (burning, light pain) the Priesnitz compress is sufficient; when there is some discomfort hot flaxseed poultices or a hot-water bag can be applied to the epigastrium for one or two hours, morning and afternoon.

If seven days after bleeding the patient is perfectly comfortable the following diet can be ordered for the second week:

*Eighth and Ninth days:*

- 7 A.M. 200 gm. milk and 50 gm. of sweet cream with sugar.
- 9 A.M. Farina cooked in milk in double boiler, served as a pap.
  - 1 soft-boiled egg.
  - 1 slice of dry toast with butter.
- 12 M. 2 soft-boiled eggs.
  - Oatmeal cooked in milk in a double boiler for two hours and served strained with butter.
  - 1 slice of dry toast with butter.
- 3 P.M. 200 gm. of milk.
  - 50 gm. of sweet cream.
  - 2 zweibacks with butter.

- 6 P.M. Rice cooked in milk for two hours in a double boiler.  
 2 soft-boiled eggs.  
 2 slices of toast and butter.
- 9 P.M. 200 gm. milk.  
 50 gm. cream.  
 Zweibacks if desired.

If the patient awakens in the course of the night he can be served with 200 gm. of milk.

*Tenth, eleventh and twelfth days:*

- 7 A.M. 200 gm. of milk.  
 50 gm. of cream.  
 3 zweibacks with butter.
- 9 A.M. Farina prepared as above.  
 1 scrambled egg.  
 2 slices of toast with butter.
- 12 M. 50 gm. of either minced veal fried in butter, minced lamb, or minced chicken.  
 2 tablespoonfuls of mashed potatoes with butter.  
 Spinach or carrots in purée form.  
 2 slices of toast with butter.
- 4 P.M. 200 gm. of milk.  
 50 gm. of cream.  
 3 zweibacks with butter.
- 7 P.M. Cereals.  
 2 soft-boiled eggs.  
 2 slices of toast and butter.  
 Spinach or carrots.
- 10 P.M. 1 cup of warm milk.

*Thirteenth and fourteenth days:*

- 7 A.M. Milk and cream.  
 2 zweibacks.
- 9 A.M. Cereal.  
 2 soft-boiled or scrambled eggs.  
 Toast and butter.
- 12 M. 100 gm. thickly prepared and strained barley soup.  
 75 gm. scraped beef or chopped chicken or calf's brain or boiled fish.  
 100 gm. mashed potatoes, spinach, carrots or green peas or the flowers of cauliflower, all in purée form.  
 50 gm. farina or rice pudding.  
 1 stick toast if desired.
- 4 P.M. 200 gm. milk with 50 gm. of cream, flavored with cocoa if desired.  
 3 zweibacks with butter.
- 7 P.M. 2 eggs (soft-boiled).  
 Toast and butter.  
 Custard.
- 10 P.M. Milk and cream.

At the beginning of the third week after the hemorrhage the patient is allowed to leave the bed with the understanding that he must rest the greater part of the day reclining on a couch.

Diet for third week:

7 A.M. Milk-cream and toast (flavored with cocoa if desired).

9 A.M. Cereals.

2 soft-boiled or scrambled eggs.

Dry toast and butter.

12.30 Cereal; soup; meats—such as chicken, fish, veal, lamb, 100 gm., and if patient can chew well the meat must not be chopped.

100 gm. mashed potatoes with butter.

Vegetables as in preceding week.

Apple-sauce and light puddings.

4 P.M. Milk or cocoa or light coffee or tea with milk and zweibacks.

7 P.M. Eggs or boiled unsalted and lean ham.

Cream cheese.

Custard.

Toast, butter, cooked vegetable.

10 P.M. Milk and cream.

The second and third week the patient is overfed; with the object of replacing the weight lost, and if possible he should even gain weight.

During the fourth and fifth week the patient is allowed to leave the house for short walks; short rests are enforced after light meals and one or two hours' rest after the chief meals.

Diet is the same as in the third week, with larger quantities if desired by the patient. The following additions are allowed:

Vegetables: Baked potatoes, asparagus tips, string beans, Brussels sprouts.

Fruits: Prunes in purée form, cooked cherries, cooked pears in purée form.

White bread one day old and not toasted.

During the sixth week longer walks are allowed and one hour's rest only is required after the main meal. The diet is so arranged as to be fully suitable to the time when the patient is allowed to follow his occupation.

He gets his first meal at 8 A.M., consisting of a baked apple with sweet cream, 2 eggs, cereal, roll with butter, light coffee, tea or cocoa.

Noon meal depends on whether the patient has two hours' time, so as to take his main meal and rest an hour after, or only one hour, necessitating a light lunch.

Medicinal treatment, when feeding by mouth, is begun on a fasting stomach, 10 to 20 gm. of bismuth subnitrate thoroughly mixed in 150 gm. non-sparkling carbonated water (Vichy Celestins)

sipped slowly a half-hour before breakfast. Such a mixture serves as an antacid, is mildly hemostatic and coats the stomach.

After each feeding the Bourget method of using alkalies has been found by us to be very efficacious. Bourget reasoned that a solution of bicarbonate of soda when given on a full stomach passes through the fold of Retzius directly to the pylorus into the duodenum, from whence it regulates the opening of the pylorus, overcoming the spasm and causing a more rapid emptying of the stomach.

This property of bicarbonate of soda solution indicates that the antacid effect of the drug does not lie in its concentration but in its reflex action from the duodenum. It is therefore not necessary to use bicarbonate of soda in doses large enough to neutralize all the acid, which would be injurious. Bourget found that 1 per cent. of bicarbonate of soda solution is enough to diminish the acidity and overcome the spasm of the pylorus. This is administered not only at the height of acidity but whenever the patient has pain or pyrosis. It is given well diluted, to be sipped slowly from one-half to one hour after light meals and one to two hours after a heavy meal.

The original formula is the following:

Sod. bicarb., 1,  
Sod. phosph., 0.3,  
Sod. sulph., 0.2,

to be dissolved in a half glass of water. If this method of administering the alkaline treatment is not fully sufficient to overcome pyrosis or pylorospasm it may alternately be replaced by the following powder:

Natr. bicarb., 1,  
Magnes carb., 0.5,  
Natrii citrici, 0.5,

dissolved in a half glass of water and administered as above.

If, on account of the excessive milk and the alkalies, diarrhea is troublesome we can, besides the morning dose of bismuth, add 1 of bismuth to every second powder.

If constipation is the troublesome factor the morning dose of bismuth should be reduced to half the quantity or given in suspension with olive oil. In order to improve the taste the emulsion is given in the following formula:

Bismut. subnitrate, 10,  
Olei olivarum, 15 to 20,  
Pulv. acaciæ, q. s.  
Aqua amygdal., dulcis ad 100.

Sig.—To be taken every morning.

As the symptoms subside, which is usually the case at the end of the first week, the patient takes the alkaline powder in a full glass of carbonated water, one-third of which is sipped slowly a half to one hour after each meal.

In most cases the outlined medicinal treatment suffices. Rarely



pylorospasm and pyrosis during the first few days necessitate the use of atropin sulphate, 0.0005 to 0.00075 intramuscularly twice daily or extract. belladon., 0.02 in suppositories twice daily. This is especially useful in vagotoniacs.

Of equal importance to the treatment outlined thus far is an understanding of the general management of the patient. Particular attention must be paid to the hygiene of the mouth. So long as no food by mouth is given, frequent rinsing of the mouth with a mild alkaline is very essential and chewing of paraffin wax. When feeding is begun rinsing of the mouth after each meal does away with the sour taste after taking milk.

A sponge bath should be given twice daily; passive movements and light massage are essential. We should see to it that the patient spends a restful night. Often intestinal distention is a disturbing factor and is best overcome by a saline enema before relaxing.

When the patient resumes his work the dietetic regime outlined for the sixth week should be adhered to for at least six months. Alkaline water (Vichy) should be taken after meals, 150 gm. The patient is cautioned against nervous excitement and physical overwork, and if a smoker he is made to give up or greatly reduce the use of tobacco. After the sixth month raw fruit in the form of a ripe banana, ripe apple peeled and well chewed or pears may be allowed. Fruits containing seeds, as well as spicy food and alcoholic beverages, should be interdicted.

The treatment of bleeding ulcers outlined above has proved valuable in most clinics.

In 1904 Lenhartz, of Hamburg, expressed the view that the extreme sparing diet advocated by Leube is not only not conducive to healing of the ulcer but prevents healing and may cause formation of new ulcers. The prolonged starvation, he believes, causes secondary anemia, and as the food allowed is insufficient to bind the free acid, the factors for the non-healing and formation of new ulcers are thus given.

Again, the cases of ulcer where hyperacidity, pylorospasm, benign stenosis or other gastric complications lead to secondary anemias need individualization, as described below, in order to bring about improvement or, if possible, cure.

The entire Lenhartz dietetic regime seems to us to bear criticism. Meat is allowed too early, with the idea of binding acidity. While correct in principle it is also true that meat stimulates more acid secretion, especially in the second phase of digestion (chemical phase, Babkin). In order to give plenty of calories, according to Lenhartz, eggs are given in very large quantities and in a form which must necessarily become obnoxious to the patient. He omits fat, which in the form of sweet cream is rich in calories, and diminishes acidity reflexly from the duodenum and is not irritating at all. It seems to us that for the reasons outlined the Lenhartz treatment has lost

its popularity, although it originated in the mind of such a great authority.

Patients with *ulcus ventriculi* who never had hemorrhages and who periodically come to us with pain, hyperacidity and hypersecretion and various degrees of motility disturbances are the cases for whom modifications in the method of treatment have not been lacking. The original strict method of von Leube that the diagnosis of *ulcus ventriculi* spells absolute rest in bed for from two to three weeks, and extreme caution in feeding, as outlined in cases of gastric bleeding, had to undergo changes for obvious reasons.

Most authors have sought to subdue the existing functional disturbances of the stomach, thereby favoring the healing of the ulcer, and all have registered favorable statistics. Judging by the improvement of the patients they were amply justified. Lasting results were unfortunately not obtained in a marked percentage of cases, so that the validity of internal treatment of ulcer has of late been questioned. Such skepticism and reaction seem to us to arise from the fact that the therapeutic procedure and results are not preceded by investigation as to the pathological status of the ulcer when treatment is begun, and the changes that took place in the ulcer and its effect on the functions of the stomach when the patient is discharged improved or cured.

Leo Schuller and Hamburger were first to utilize the roentgen rays and other clinical methods for the study of the effects of treatment, a very worthy addition to the therapeutics of *ulcus ventriculi*.

In order to understand what results are to be expected of treatment we must picture to ourselves the existing pathological process. It is known that an ulcer of the stomach may exist on the mucosa and submucosa, eroding the bloodvessels and causing bleeding. This usually heals, leaving superficial scar tissue, sometimes not even recognizable on the postmortem table. If such an ulcer does not heal the destruction of larger vessels, with the resulting local thrombosis and necrosis, causes a deeper ulcer, reaching the serosa and even perforating beyond, an occurrence fortunately not frequent. It is therefore not so difficult to direct the treatment and prognosticate a bleeding ulcer. In most cases after a successful course of treatment the symptoms may never return; on the other hand, recurrence of hemorrhage indicates surgical treatment.

In chronic recurrent non-bleeding ulcers the healing process is that of connective-tissue formation. It was pointed out by Orth that ulceration may be formed on the smooth base of the newly formed tissue—an explanation for the recurrence of symptoms.

With each recurrence there is additional connective-tissue formation. In very many cases the connective-tissue formation is of moderate extent so that no stenosis results even if the ulcer is situated at either ostium of the stomach. In these cases the motility disturbances are dependent on the hypersecretion and hyperacidity.

In other cases the connective-tissue formation is excessive, resulting in stenosis if near the ostia and very marked motility disturbances if even on the lesser curvature. The pathological changes being of such a varying degree we consequently must assume that the mode of treatment would have to vary accordingly.

Of equal importance for successful therapeutic measures in ulcer ventriculi is an exact knowledge of the disturbed functions of the stomach causing the existing symptoms.

The main and most easily diagnosed class of patients who present themselves with hyperacidity, hypersecretion, pain, disturbed motility of various degrees of periodicity, etc., are best treated by one of the following methods:

First to deserve mention, because of its efficacy and simplicity and because it is based on sound reasoning and experience, is the Sippy<sup>1</sup> method. The underlying principle of this treatment is the complete subduing of the free HCl.

An important adjuvant to the successful medical treatment of gastric ulcer has been made by Einhorn in the form of duodenal alimentation. Methods of introduction of the tube have been described by Einhorn,<sup>2</sup> Gross<sup>3</sup> and Held, Holzknacht<sup>4</sup> and Lippman.

Smithies<sup>5</sup> has advocated a course of treatment of ulcer ventriculi which deserves mention.

The method advocated by Stone<sup>6</sup> consists in the avoidance of carbohydrates in order to prevent fermentation.

Of late there has been an inclination on the part of some to advocate the ambulatory treatment of ulcer ventriculi, claiming good results. We decidedly question whether many of the cases so treated were really ulcers. However, the economic condition of the patient may be such that a compromise becomes necessary, though, on general principles, this is not proper. We must be clear in our mind as to the exact underlying functional disturbances of the stomach and be assured that ambulatory treatment will yield the desired success.

Individuals suited to such treatment are mostly of the sthenic type, in whom the gastric disturbances have a tendency to disappear as soon as a bland diet is resorted to and who have long intervals of freedom from symptoms. Finally, even when the symptoms are present the chemical as well as the roentgen-ray findings show a moderate degree of disturbance.

Of what does the ambulatory treatment consist? We insist on our patient adhering strictly to the following rules:

Restriction of work as much as possible for the first two weeks; to rest for from one-half to one hour after each meal, depending on

<sup>1</sup> Jour. Am. Med. Assn., May 15, 1916.    <sup>2</sup> Med. Rec., 1910.

<sup>3</sup> Jour. Am. Med. Assn., August, 1915.    <sup>4</sup> Munch. Med. Woch., September, 1914.

<sup>5</sup> AM. JOUR. MED. SC., 1917, p. 54.

<sup>6</sup> Jour. Am. Med. Assn., January 25, and September 30, 1916.

the quantity taken; to take his meals more frequently and obey strictly as to quality and quantity. All mental excitement and bodily fatigue must be avoided. A Priesnitz compress over the abdomen should be applied overnight and a light flannel abdominal binder should be worn for the day during the cool months.

Diet: The first week, if there is marked pain, the patient is allowed, until pain subsides, lukewarm milk every three hours, daily quantity between  $2\frac{1}{2}$  and 3 liters. For patients who do not tolerate milk alone we may add either some lime water to the milk or, mornings and evenings when the patient is at home, add a fine cereal (hominy) to the milk. We can also increase the nutritive value of the milk by adding a half-pint of sweet cream during the twenty-four hours.

Second Week—Morning: One or two soft-boiled eggs, cereal, milk soup, one cup of milk. 10 A.M.: One cup of milk with cream, two zweibacks and butter. Noon: One or two eggs, cereal, milk soup, one cup of milk. 4 P.M.: One cup of milk, two zweibacks and butter. Evening: Two eggs, cereal, milk soup, milk with cream two zweibacks and butter. 10 P.M.: One cup of milk.

Third week: Besides the foodstuffs mentioned in the first two weeks, the patient gets 60 gm. of scraped beef or minced veal, or scraped, cooked, unsalted ham, 50 gm. of mashed potatoes, or spinach or carrots in purée form and toasted white bread.

Fourth week, we add cereal puddings made with butter, milk or cream (non-flavored), and at the end of this week apple-sauce or baked apples.

Fifth week, we add to the list of meats, boiled chicken, chopped, sweetbreads or fish, and gradually increase the quantity of meat to 100 gm.

Medicinal treatment consists in the use of alkalies after meals, during the month of the treatment Karlsbad Muhlbrunn, 250 gm. taken warm one-half hour before breakfast.

Such a course of treatment, if successful, should teach the patient how to live hygienically and dietetically in order to avoid future recurrences.

The treatment outlined thus far is sometimes unsuccessful. If so, the cause is to be sought and treated, if possible. Among the determinable factors interfering with the healing of the ulcer and often causing new ulcer formation are:

1. Vagotonia.
  2. Congenital or acquired enteroptosis, with its resulting atony.
  3. Secondary anemia.
  4. Gastric catarrh—as gastritis hyperacida or sub- or anacidity.
  5. Ulcer coexistent with sub- or anacidity.
  6. Benign stenosis.
1. Vagotoniacs, with their tendency to hypersecretion, hyperacidity and hyperperistalsis, even without organic disease of the

stomach, will be so much more subject to persistent gastric disturbances when ulcer has formed.

Treatment will have to be directed to the vagotonia. In addition to careful diet and necessary alkaline treatment the patient should receive appropriate hydrotherapeutic measures during treatment of the acute symptoms. Cool sponge bath in the morning or lukewarm half-bath with cool shower bath and Priesnitz compresses overnight—well-fitting abdominal binders are necessary.

Medicinally atropin sulphate (0.0005 to 0.0001), subcutaneously once or twice daily until the physiological effect is reached, or in the form of extract of belladonna, 0.01 to 0.02, in powder one hour after meals, or 0.02 to 0.03 in the form of suppositories twice daily. Belladonna and its alkaloid had a specific effect in paralyzing the vagus, thereby subduing the excessive gastric secretion and peristalsis. Vagotoniacs must adhere to a non-irritating and nourishing diet for the rest of their lives as well as to the hygienic and physical measures involved.

2. In the congenital enteroptotic it is of the utmost importance that no ambulatoric treatment be attempted. Absolute rest has here the double object of giving the ulcer a chance to heal and at the same time letting the patient gain in weight—an indispensable factor in these cases.

During the first few days frequent feedings (one or two hourly) are not desirable, as the motility is very markedly delayed. As retention of food is a greater factor in exciting secretions than the largest doses of alkalis can neutralize it is obvious that the small quantities of food (two or three ounces) every three hours for the first three or four days is the better plan. When we proceed with larger quantities it is best to administer the food in the form of semisolids like thickly prepared cereals in milk, later vegetable purée; during the third week scraped beef or chopped meats, and later jellies, cooked fruit in purée form, etc. Emphasis is especially laid on the use of more solid food because excessive amounts of fluid (as is the case with milk diet) cause sagging and more loss of tone of the stomach musculature.

Lying on the right side after each meal for half an hour will facilitate the emptying of the stomach. If during the first week, notwithstanding the small quantities of food taken, there are signs of gastric retention, lavage of the stomach with one-half to one pint of alkaline water is to be employed, to be entirely returned, mornings and before retiring, for the first two or three days. For another two days, mornings only, using but half a pint of water, and, if necessary, for another two or three days the dry method of lavage (Boas), which consists in the introduction of the tube and obtaining the contents by expression.

Medicinally: Tonic treatment in the form of iron, arsenic and strychnin or phosphor, arsenic and stryptsin (serum neurasthenique) intramuscularly.

The acquired gastro- or gastro-enteroptosis is due to the fact that the patient cannot or fears to partake of sufficient food for an extended length of time. The resulting gastric symptoms are more due to the existing atony of the stomach than to the ulcer proper. Prolonged unsuccessful treatment for ulcer leads both patient and attending physician to despondency, and surgical intervention is advised. When the tone of the stomach is lost surgical treatment for the ulcer does not, as a rule, yield the desired results. The treatment in general corresponds to that outlined for congenital cases.

Prognosis as to improvement of the tonus is here very much better than in the congenital type. Well-fitting abdominal binders are very useful in both varieties.

3. Secondary Anemia. Patients with atony of the stomach secondary to ulcer often present themselves with marked secondary anemia, so that the hemoglobin may be as low as 50 per cent., even 40 per cent. Here active treatment by means of one or more blood transfusions must be instituted. Treatment that ignores the anemia not only fails to heal the old ulcer but is even conducive to formation of new ulcers.

4. Gastric Catarrh. There are cases in which we find in addition to the ulcer definite evidence of coexisting gastric catarrh. In most of these sub- or even anacidity is present; in a lesser number hyperacidity is found. This catarrh, as mentioned elsewhere, may be the result of stagnation and fermentation, of food secondary to the ulcer or the individual afflicted with the ulcer has at the same time a circulatory or metabolic disease or an alcoholic gastritis. When the catarrh is directly secondary to the ulcer the outlined ulcer cure, with modifications to be mentioned, is very beneficial.

In sub- or anacidities large doses of alkalies are superfluous. The alkaline saline waters are beneficial and given in the following manner: Mornings, one-half to one hour before breakfast, 300 to 400 gm. of an alkaline sodium chloride water (Homburg, Karlsbad, Sprudel or Hawthorn Saratoga water) taken hot serves as an auto-lavage. Half the dose can be taken half an hour before supper. If this alone is not sufficient, lavage of the fasting stomach with 1 or 2 pints of a normal saline solution may be resorted to for about a week.

Meats should not be allowed in any form until all symptoms have disappeared, and then for a long time only finely chopped, because mucus even in small quantities interferes with chymification.

After meals, calcium carbon, 0.3, is to be given. HCl should not be employed, notwithstanding the low acidity, nor should spicy or irritating foodstuffs be allowed, as in achylia or ordinary gastritis anacida.

When hyperacidity is a factor the alkaline treatment, as outlined by Sippy, is very efficacious. In addition an alkaline water (350 to 400 gm.) on a fasting stomach, and half the morning quantity at

5 P.M. for one month, or lavage of the fasting stomach with an alkaline solution.

When metabolic or circulatory disease, besides the ulcer, is responsible for the catarrh the ulcer cure alone will only bring partial benefit unless appropriate curative measures are taken.

In these cases an annual spa cure is highly recommended, for one month, with mild saline waters for sub- or anacidity, and alkaline water when hyperacidity exists. When the patient cannot afford a spa, home treatment should be substituted.

5. For patients with ulcer ventriculi who present themselves with sub- or anacidity without catarrh, treatment must be modified according to the underlying cause of the condition. This sub- or anacidity has been attributed by most authors to a tiring of the peptic glands, due to their prolonged hyperactive secretions. This theory is plausible but cannot be proved.

We believe, as mentioned elsewhere<sup>7</sup> that other factors may be responsible for the sub- or anacidity. Vagotoniacs often change during or after middle life into sympathicotoniacs, so that hyperacidity (vagotonia) during early adult life changes to sub- or anacidity (sympatricotonia). Another factor is extensive perigastric adhesions which when in the region of the pylorus mechanically prevent closure of same, thereby allowing the duodenal contents to regurgitate; also, adhesions to other adjacent organs diminishing contractability of the entire stomach and with this the secretions. Our reasons (sympathicotonia, adhesions) for the cause of sub- or anacidity would tend to explain why the ulcer symptoms persist notwithstanding the cessation of hyperacid secretion.

If the theory of the tiring of the peptic glands held good we ought to expect healing of the ulcer and disappearance of symptoms, which is not the case. It seems to us important to try to determine the causative factors of the sub- or anacidity in order to apply proper treatment. When sympathicotonia is a factor we must direct our therapeutic attention to the nervous system. Regulation of life, hydrotherapeutics and avoidance of exciting factors are as essential as the treatment of the ulcer proper. Spicy and seasoned or irritating foods must be avoided. The diet is almost the same as for ulcer with normal or hyperacidity. If examination of the stool shows that meat is not well digested it should be given chopped and well done, or left out of the diet list for one or two days each week; fats, carbohydrates, and vegetable purée should constitute the main articles of food. HCl should not be given; an alkaline saline water (Saratoga, Homburg, etc.), can be given, a wineglassful thrice daily after meals. Parathyroid tablets (0.001 to 0.01) after meals may be tried.

When gastric adhesions are the cause of the sub- or anacidity in ulcer ventriculi the treatment of the ulcer proper must be conducted

<sup>7</sup> Gross, Held: Interstate Med. Jour., 1917, No. 4, vol. xxiv.

as if we were dealing with normal or hyperacidity, as already described. If symptoms persist and are more or less continuous, local heat, either in the form of hot flaxseed (applied one hour mornings before getting out of bed and one hour before retiring) or fango (applied a few times a week) or heat in the form of diathermia should be instituted. Such treatment does not break up adhesions but it helps toward restoration of the gastric functions. If it is without effect, surgery is to be resorted to.

The operative interference has its beneficial effect, chiefly through gastro-enterostomy. Separation of adhesions is often technically impossible; strenuous efforts to do so have often led to postoperative emboli, and even if successfully separated adhesions too often reform. We see therefore that favorable results in gastric adhesions are dependent on relief of abnormal tension in the stomach and functional restitution.

6. Treatment of Delayed Stomach Action. A clear understanding of the pathological condition in the stomach which causes delay in the emptying is very essential. This delay is seldom due to an indurated ulcer in the region of the pars media (tube) on the lesser curvature. An ulcer in that location causes frequent vomiting. This may be due to a pylorospasm, with relaxation of the cardia. When delay in emptying occurs with an induration in that location, atony of the gastric musculature, with accompanying fermentation and pylorospasm, are the underlying factors. In very rare cases a second indurated ulcer in the pylorus may be the cause of delayed emptying, and medical treatment rather than surgical intervention should be instituted.

An indurated ulcer in the pylorus proper is the most frequent cause of delay. Not only are cases amenable to medical treatment when but small residues are found in the stomach twelve hours after a meal, but even when twenty-four-hour and even longer retentions are encountered. The reason for this is that the exit of the food is not, in most cases, prevented by the connective tissue filling out the entire pylorus. Such conditions call absolutely for surgical intervention.

We refer to cases where the associated atony of the stomach or the marked pylorospasm or pyloritis prevents the normal passage of food into the small intestine. The treatment will depend on the degree of stagnation as determined by the known motility tests, the chemical findings and the tone of the gastric musculature as demonstrated by the roentgen rays.

In cases in which twelve hours after a Bourget-Faber meal, or a rice and raisin meal, we obtain from the fasting stomach only a moderate quantity of fluid contents holding in suspension macroscopically visible food particles, with a high acidity and non-rancid odor, the following procedure yields very effective results:

The patient is put to bed for at least one week. For the first three



days a morning lavage with  $\frac{1}{2}$  pint of warm bicarbonate solution ( $\frac{1}{2}$  teaspoonful to 250 gm.) to be returned by expression is indicated. For another two days the sound should be introduced on a fasting stomach and the contents obtained by expression without lavage, the so-called dry lavage of Boas. After that, for a month or longer depending on the subjective feeling, the patient should take 250 gm. of a warm alkaline water one-half hour before breakfast, sipped slowly (autolavage).

The most important factor is a proper diet. Being aware that the grinding power of the stomach is disturbed, acid secretions increased and the passageway narrowed, food of such nature must be given as needs the least chymification, does not excite gastric secretion and can even pass the narrow pylorus. During the first week, in bed the diet must be of a nature to spare the organ, and consists of the following:

For the first three days:

7.30 A.M. (half an hour after the lavage or the alkaline water):

120 gm. parboiled skimmed milk.

40 gm. warm water.

20 gm. lime water.

9.00 A.M. 120 to 150 gm. of well-cooked and strained barley gruel.

11.00 A.M. Same as 7.30 A.M.

1.00 P.M. Cream of wheat finely suspended in skimmed milk, half-diluted in water, salt and sugar to improve the taste, 150 gm.

3.00 P.M. Same as 9 A.M.

5.00 P.M. Same as 7.30 A.M.

9.30 P.M. Same as 1 P.M.

During this time 1 pint of a 5 to 10 per cent. glucose solution can be administered per rectum by the drip method twice daily.

After the third day and to the end of the first week:

7.30 A.M. 200 gm. cocoa cooked in water and served with one-half parboiled skimmed milk.

9.30 A.M. 200 gm. barley gruel.

1 gm. soft egg (put in cold water and removed just as soon as the water has reached the boiling point).

12.30 P.M. 250 gm. cream of wheat with whole milk.

3.00 P.M. 200 gm. parboiled milk with one-half lime water.

5.00 P.M. 1 gm. egg (as above).

7.00 P.M. Cocoa (as above).

1 gm. egg.

9.30 P.M. 250 gm. parboiled milk and one-fifth lime water.

If the patient is comfortable we may allow, the last two days of the first week, 1 zweiback three times daily. After each feeding the patient should lie on his right side for half an hour to an hour.

The second week, if the patient has improved considerably, he is

allowed to leave the bed for the greater part of the day, only resting on his right side for from one-half to one hour after meals. The intervals of feeding are lengthened to three hours, and the following diet is ordered:

- 7.00 A.M. Alkaline water.
- 7.30 A.M. 250 c.c. warm parboiled milk.  
1 egg.  
2 slices of toast with butter.
- 10.30 A.M. 250 gm. strained oatmeal served with warm milk.  
1 egg (soft-boiled).  
1 slice of toast with butter.
- 1.30 P.M. A cereal cooked in milk; second half of week mashed potatoes with butter.  
Spinach or carrots in purée form, butter or cream added to increase nutritive value.  
1 poached egg on toast or with the spinach.  
1 slice of toast.
- 4.30 P.M. Weak cocoa and 2 zweibacks with butter.
- 7.30 P.M. A cereal with milk.  
2 eggs, soft-boiled.  
150 c.c. parboiled warm milk.  
1 slice of toast with butter.

During the third and fourth weeks the patient may assume his occupation, but must be told to adhere strictly to all rules of diet. Alkaline water to be continued.

Breakfast: 2 soft-boiled or poached eggs; 2 slices of toast and butter; 200 gm. weak cocoa or parboiled milk.

Lunch should form the chief meal and consume at least from one to one hour and a half, including time for rest. Boiled chicken, chopped or minced veal or beef, rare and fried in butter, or soft lamb thoroughly chewed, or well-cooked fish, from 60 gm. to 120 gm., gradually increasing if condition improves. Mashed or baked potatoes, 75 to 100 gm. Carrots or spinach or cauliflower or green peas in purée form. Custard, farina, rice, tapioca pudding and apple-sauce, 50 gm.

4.00 P.M. cocoa and zweibacks.

Supper: Cereal in milk; omelette souffle or cereal pudding, with eggs and butter. Baked apple or ripe banana, with cream, dry roll or toast.

As to medicinal treatment it is our experience that the carrying out of the above dietetic regime will not necessitate any medication. However, should pyrosis be a factor an alkaline non-sparkling Vichy (Celestins, Saratoga), one wineglassful with meals, can be given. If this alone is not effective, magnes. ustæ, 1 gm., or bicarbonate of soda, 1 gm., can be added to the water. When there is reason to believe that pylorospasm exists (vagotonia) or spastic constipation,

extract of belladonna, 0.02 in the form of suppositories, can be employed twice daily.

If anemia and general loss of tone is a factor, sodium cacodylate, with or without iron and strychnin intramuscularly (0.03 in ampoules), 25 to 30 injections; also appropriate hydrotherapeutics are of service.

After the fourth week a list should be written down of foods the patient is allowed to have. For example:

**Meats:** Chicken, squabs, lean fish, lamb, veal, ham non-salted and cooked, beef, white of turkey, eggs.

**Vegetables:** Spinach, asparagus, cauliflower, carrots, turnips, Brussels sprouts, string beans, green peas, mashed potatoes.

**Fats:** Butter, 40 per cent. sweet cream.

**Fruits:** Cooked fruit—apples, pears, prunes, peaches, cherries. Also ripe bananas, melons without seeds.

**Fluids:** Milk, cocoa, buttermilk, zoölack, weak coffee or tea with milk, non-sparkling alkaline waters.

**Cereals:** Farina, tapioca, sago, rice, oatmeal, barley, cream of wheat, cornflakes.

All meats should be served plainly cooked, broiled or fried in butter, non-spiced, quantity not to exceed 150 gm. Eggs, soft-boiled, poached or scrambled.

**Vegetables:** Only in purée form, with butter, milk or cream.

**Fruits:** Peeled, stewed or baked.

**Fluids:** Those named in small quantities not exceeding 200 gm.

**Cereals:** Well-cooked, served with milk, butter or cream or in the form of custards and puddings.

The patient should be instructed that if symptoms of discomfort set in he must report at once for examination, as by so doing only can recurrence and progression of the disease be obviated.

After the main meal, lying on the right side for at least half an hour is essential.

The quantity of fluids should be restricted and no fluid outside of milk or cocoa should be taken with meals.

A well-fitting abdominal binder is beneficial where atony is an important factor in the course of stenosis.

The more advanced class of incomplete pyloric stenosis, as the result of a callous ulcer of the pylorus, which manifests itself by marked signs of gastric stagnation, requires a still more stringent method of treatment. It must be remembered that the underlying pathological condition causing the symptoms lies as much in the hyperemic gastric mucosa and pyloritis as in the callous ulcer itself. The treatment therefore must be directed toward a complete rest of the stomach until subjective and objective symptoms disappear.

The patient should stay in bed for from three to four weeks. A thorough lavage of the stomach with a mild alkaline solution should initiate the treatment. All stagnated food, as well as the tenacious

mucus, is thereby removed. No food by mouth is allowed for at least four to seven days. During that time rectal alimentation is to be administered, more for the purpose of carrying fluid to the system than for nutrition.

Unlike the ordinary ulcer treatment we must seek to supply the patient (as a rule in a state of emaciation) with as many calories per rectum as is possible. This may be accomplished by glucose solution (10 per cent.), 1 pint twice daily, to which 1 ounce (30 gm.) of 50 per cent. alcohol can be added (Smithies). One nutritive enema should consist of peptonized milk, 1 pint, and 1 pint of 50 gm. sweet cream; 1 gm. pancreatin; 5 gm. bicarbonate of soda suspended in 1 pint of normal saline solution. This enema should be given at 8 A.M., 12 M., 4 P.M., and 9 P.M. All nutritive enemas are to be given at body temperature and by the drip method.

The first rectal feeding should be preceded by a cleansing enema. In order to prevent intestinal irritation, which is often most marked during the night, 15 to 20 drops of tincture of opium can be added to the last nutritive enema.

During the period of rectal feeding the mouth hygiene described above is to be observed. In order to quench the thirst small quantities (60 gm.) of distilled water may be allowed four or five times daily after the first lavage; if pyrosis is annoying, even during the fasting period an alkaline powder should be added to the water.

When mouth feeding is begun we must allow food only in such form as would most easily pass the pylorus, and for a time neither demand motility nor invoke digestive activity of the stomach. Carbohydrates in a fluid form are most appropriate, because they need no stomach digestion, they are nutritive, and prevent starvation acidosis even if the patient is underfed; furthermore, as carbohydrates do not bind the free acid, the latter serves to open the pylorus.

Proteins and even some fat can be administered in the form of very soft-boiled eggs, because in such form they pass the stomach at once (Cannon). Skimmed, well-diluted milk may also be allowed.

Carbohydrates are administered in the form of thin, well-prepared and strained barley soup or in the form of cream of wheat or strained oatmeal. Quantity of fluid at each feeding should not exceed 100 to 120 gm. during the first four to seven days of mouth feeding. Add to this three or four eggs either alone or shaken up in the milk.

Feeding should be given every three hours from 7 A.M. to 10 P.M., in order to give the stomach a chance to empty itself between each feeding. Lying on the right side for at least half an hour after each feeding is very essential. During this week one or two rectal feedings with glucose solution is to be continued.

If symptoms indicate that the stomach does not empty itself, causing disturbances, especially during the night, dry lavage (Boas)

before retiring, followed by a warm alkaline drink (200 gm.) to serve as an autolavage and to neutralize the acidity, is very efficacious.

If toward the end of the second week motility or secretory disturbances manifest themselves, despite careful treatment, duodenal feeding is to be employed, first ascertaining that the duodenal tube has reached the small intestine. This is continued for from ten to twelve days and followed for three or four days by a milk-cereal diet.

During the third and fourth weeks, if the condition of the patient permits, the diet list outlined for the second week in milder cases of pyloric stenosis may be used. During his stay in bed, Priesnitz compresses to the abdomen, sponge baths morning and evening and light general massage should be employed.

Medicinal: Sometimes during the first and second week the symptoms of pylorospasm necessitate atropin sulphate (0.0005 to 0.001) hypodermically twice daily, or suppositories of extract of belladonna (0.02) also twice daily.

During the last two weeks of treatment some advise the use of strychn. nitr. (0.001) hypodermically once or twice a day as a muscular tonic.

After four weeks the patient is allowed to leave the bed, with directions that food taken shall be well prepared in purée form, bread toasted (preferably milk-toast), and all food is to be thoroughly chewed. Fluid should be restricted.

Feeding should be in quantities not to cause fulness after a meal and should be given every three or four hours. Lying on the right side after the main meal is very important. This meal, if possible, should be had at the noon hour. These directions ought to be adhered to for an indefinite length of time—even for life.

Gastric lavage will not be needed if the rules outlined are followed. The first signs of motility disturbance, however, call at once for a lavage before retiring (at least three hours after the last meal) and a moderate restriction of diet for a few days in order to prevent recurrence.

If the patient can afford an appropriate spa or a cure at home for four weeks every year it is very beneficial. A well-fitting abdominal binder, especially for asthenic individuals, should be ordered.

Einhorn has advocated a special instrument for stretching the stenosed pylorus. We have no experience in the use of the instrument. We feel, however, that blind stretching is not a desired surgical procedure. If the stenosis is such as to require instrumental interference, surgical intervention is the safer and by far the more rational procedure.

**DELAY IN THE TREATMENT OF CANCER.<sup>1</sup>**

BY CHARLES E. FARR, M.D.,

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DURING a period of about one and a half years, 103 cases of malignant disease entered the Cornell or First Surgical Division of the New York Hospital under the charge of Professor Gibson. At his instance a careful record was kept in each case of the duration of symptoms and the various reasons for delay in seeking treatment. Of the cases, 41 were classed as external, that is, the growth was visible or easily palpable, 60 were internal, 2 were not classified. Of the internal growths, 6 were of the rectum, 8 of the uterus, 3 of the cervix, 2 of the bladder and 2 of the prostate.

Of the total number of cases the average period from the onset of symptoms to the first consultation with a physician was 3.19 months and the average period from this time until the entrance into the hospital was 8.7 months. This gives a total of 11.89 months, practically a year, in the average case, from the onset of symptoms to the entrance into the hospital.

An attempt was then made to group the cases according to their curability on entering the hospital. This was done by Dr. Kenneth Johnson, house surgeon at the time, as it was felt his opinion would be unbiased. The classification adopted was: *Curable, Probably Curable, Operable, Inoperable and Incurable*. The advice of the physician first consulted was then considered in relation to each case of the various groups, being classed as right or good when he urged the hospital and an operation, wrong when he did otherwise.

The question of diagnosis by the physician was not considered.

*Curable Cases.* Of these there were 18. The advice given was right in 11, wrong in 7.

*Probably Curable Cases.* 35 in number. Right, 17, wrong 18.

*Operable Cases.* 71 in number. Right 37, wrong 34.

*Inoperable Cases.* 29 in number. Right 12, wrong 17.

*Incurable Cases.* 48 in number. Right 16, wrong 32.

Of the 101 cases classified, 44 received good advice from the first physician consulted, 47 did not.

Even if we make every allowance for misunderstanding and ignorance on the part of the patient the showing is appalling.

The data so far obtained are too meager for definite conclusions, but it is obvious that in the average case a considerable period of time is lost between the onset of symptoms and the first visit to a physician, that the physicians' advice is wrong in considerably more than half the cases and finally a much longer period after the first consultation is wasted before the patient enters the hospital.

<sup>1</sup> Read before the Society of Practical Medicine, February 21, 1917.

The data in the incurable cases would seem to bear out the ill results of the physician's wrong advice. Practically 50 per cent. came too late for a cure, and of these two-thirds had been poorly advised by their physicians.

The causes for delay in seeking surgical help are not far to seek—ignorance and fear on the part of the patient, possibly fear of losing a patient on the part of the physician. An ill-founded and careless optimism costs many lives undoubtedly. In extenuation it may be said that the average physician sees not more than 1 case of cancer a year, judging from the latest and best statistics available. It is too much to expect him to be able to make refined diagnoses under the circumstances, but he should be taught, and so should the laity, that every "lump" may be the seed or beginning of a cancer, and that an early slight operation offers far better prospects, than a late severe one.

My sincere thanks are due to Professor Gibson for permission to publish the data obtained in his service and to Dr. Kenneth Johnson for aid in tabulating them.

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## THE ANATOMICAL CHANGES AND HISTOGENESIS IN GASTRITIS GRANULOMATOSA FIBROPLASTICA.

BENIGN PYLORUS HYPERTROPHY, SIMPLE INFLAMMATORY CIRRHOSIS  
OF THE STOMACH, LINITIS PLASTICA.

BY GEORGE E. ARMSTRONG,

AND

HORST OERTEL,

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THE occurrence of purely inflammatory sclerosing thickenings of the stomach, notably in the pyloric region, which are not of congenital or cancerous origin, has received little recognition up to the present time. Indeed, this occurrence has even been questioned and denied in recent years. It is true that the early literature on the subject is little convincing, for the incompleteness with which anatomical findings were recorded and studied from Cruveilhier<sup>1</sup> to Brinton,<sup>2</sup> and in many instances even later, hardly allowed any definite opinion in this regard. The chief questions at issue were

<sup>1</sup> *Anatomie Pathologique du corps humaine*, Paris, 1835, tom. iii, p. 25 (Lyle), or, 1829-1831, tom. xli (Krompecher).

<sup>2</sup> *Diseases of the Stomach*, 1864.

whether such hypertrophic scleroses were always either congenital or, if originating in later life, simply masked a scirrhus cancer. However, in view of the more complete recent studies, particularly by Tilger,<sup>3</sup> von Sury,<sup>4</sup> Curtis,<sup>5</sup> Krompecher<sup>6</sup> and Gruner,<sup>7</sup> there can no longer be any doubt that there exist cases of localized or more diffuse, sometimes extraordinary, thickenings of the stomach, which develop during adult life and are not tumors in the usual sense of the term. The investigations of Tilger and the quite recent ones of Krompecher deal with the subject in an exhaustive manner and also review critically the previous work as well as the history of the various conceptions in this regard. It is therefore unnecessary to record these here. The article by Lyle<sup>8</sup> has also a good bibliography appended. It will only be necessary to sketch briefly once more the chief features of the disease and the various views as to its pathogenesis and histogenesis.

Anatomically and histologically these cases are characterized by a pronounced but variable thickening of the walls of the stomach, more especially of the pyloric region. This thickening involves particularly the submucosa which, even on gross examination, stands out prominently and is pale, pearly glistening and smooth. It is either purely sclerosed or more or less cellular, fibroplastic and occasionally has been reported to show endarteritic changes. The underlying muscularis shows generally marked hypertrophy. The conditions of the mucous membrane and serosa appear to show great variations. The former has been reported as hypertrophied, its connective tissue as thickened and hyaline and occasionally infiltrated with inflammatory cells; again, as superficially necrotic and the deeper portions much overgrown by inflammatory cells. The serosa has been described as edematous, with hyaline thickening, but also as little or not involved.

The interpretation of these changes has been difficult and attempted in various ways. While most observers look upon the process as inflammatory the genesis and etiology have always remained much disputed. Some bring it into definite relation to alterations or infections of adjoining structures; for instance, the gall-bladder or chronic sclerosing lesions of the peritoneum; but if such a connection exists at all its genetic relation has remained uncertain, and these ideas are certainly not applicable to many cases. Some instances have been traced to phlegmonous gastritis or ulcers, or the mucous membrane has at least been held responsible as the port of entrance or primary focus of infection. Syphilis and tuber-

<sup>3</sup> Virchows Arch., 1893, vol. cxxxi.

<sup>4</sup> Arch. f. Verdauungs Krank., 1907, vol. xiii.

<sup>5</sup> Arch. d. méd. expérimentale, 1908, xx.

<sup>6</sup> Ziegler's Beiträge, 1910, xlix, 384.

<sup>7</sup> Bulletin from the Royal Victoria Hospital, August, 1912, No. 2, p. 149, and especially p. 153.

<sup>8</sup> Annals of Surgery, 1911, No. 5, liv.



culosis have been looked upon as etiological factors, the former particularly on account of the occasional vascular changes in the submucosa. The majority of writers agree that the thickening of the submucosa is primary and leads to functional hypertrophy of the musculature.

Krompecher, on the other hand, in a study of 9 cases, traces the lesion to a general circulatory disturbance and venous stasis, which lead to edematous swelling and collagenous hypertrophy of the connective tissue of the stomach in the manner described by Unna. Muscular hypertrophy he also regards as secondary and functional. He questions, but does not deny, the inflammatory character of the lesion, but regards the disease essentially as a local manifestation of a systemic disease.

The 2 cases here reported belong to the category under discussion. The material of both was obtained during the life of the individuals by operation and the examination of the tissues, therefore, limited to these parts. However, in each case the disease seemed well localized to the removed portions, which even went beyond the affected areas, thus allowing complete examination of the local lesion and comparison with the neighboring unaffected parts.

The disease has already been discussed from the clinical standpoint with a resumé of anatomical findings in a previous paper by one of us.<sup>9</sup> We present here the detailed report of the anatomical and histogenetic characters of this lesion as based upon the last two cases observed in the Royal Victoria Hospital, Montreal.

CASE 1.—The specimen, removed by operation, represents the pyloric end of the stomach and measures 8 cm. in length. The wall is 1.5 cm. in thickness at its thickest portion, this thickening being particularly at the expense of the submucous coat. The mucous membrane showed numerous but superficial ulcerations (covered by barium), but these ulcerations did not extend into the deeper tissues. The thickened wall was firm but not of the stony hardness frequently encountered in scirrhus cancers. The serous coat was smooth and pinkish. Microscopic examination of various parts showed essentially the following lesions: The submucous coat is diffusely and densely infiltrated by lymphoid cells. This infiltration obliterates in parts the boundary of the mucosa and submucosa and becomes continuous with a similar infiltration of the lower parts of the mucous membrane, in which are also involved the lymphatic follicles by process of hyperplasia. Thus mucosa and submucosa are gradually overgrown by lymphoid cells, which rest and extend within a thin reticular tissue. In other and apparently more recently extended parts the lesion presents itself in marked perivascular lymphoid-cell infiltrations confined to the deeper portions of the submucosa while

<sup>9</sup> Armstrong: Scientific Reports of the Royal Victoria Hospital, 1916, Series B, No. 1.

its upper part and the mucous membrane appear intact. The glandular elements of the mucous membrane do not seem to play an active part in the process at all, but when they have become overgrown by lymphoid cells, and probably also have been damaged by nutritive changes, local necrosis ensues and the mucous membrane shows rather superficial ulcerations. If one now examines parts of what appear to be the well-established and older processes the lesion seems to play in and progress particularly in the submucosa. In this are also found definite arterial changes. These in the larger vessels are an endarteritis obliterans associated with thrombus formation, and even in the smaller vessels endothelial proliferation leading to thickening of their walls is evident. In these older foci there appears an irregular rather unhealthy fibroplastic proliferation displaying a tendency to necrosis and karyorrhexis. In the deeper portions of the submucosa there has thus been produced a mature thick and hyaline but unhealthy fibrous tissue. While in the upper portions of the submucosa the tissue shows greater uniformity in lymphoid cells the type becomes polymorphous in the deeper and older parts. There are lymphoid and epithelioid and occasionally very definite giant cells. Some of these may be due to thrombosed capillaries. The lesion stops rather abruptly at the muscular coat. This remains unchanged and undergoes moderate hypertrophy. The serous coat is moderately thickened by fibrous tissue, well separated from the muscular coat and shows some perivascular lymphoid infiltration, with thickening of its bloodvessels. It must be added that the operation revealed that the patient was also suffering from cirrhosis of the liver.

CASE II.—The specimen, removed by operation, consists of the pyloric end of the stomach and a small portion of the duodenum, the whole measuring 9 x 7 cm. The pylorus, to an extent of about 4 x 3.5 cm., is greatly thickened, and about 1 cm. from the ring there is a puckered depression, evidently an ulcer. Around this there is much induration of all coats, which, at the thickest point, amounts to 1 cm. This involves an area about the size of a walnut, and it is covered by smooth peritoneum, which shows much less thickening than the serous coat. Accompanying the specimen are several hard lymph nodes.

Microscopically the coats of the stomach, with the exception of the serosa, are all thickened but well differentiated. The mucous membrane is well-defined from the underlying extremely thick and fibrous submucous tissue and sits straight upon it. Only isolated thin streaks of fibroplastic and lymphoid cells are seen to occasionally extend from one into the other. Where the mucous membrane over these thickened areas is best preserved it shows hypertrophy of the mucosa with accentuation of its villous arrangement and large well-formed glands with delicate basement membrane and high cylindrical epithelium, separated by cellular septa of the tunica

propria. These areas interchange with others in which the superficial portions of the mucous membrane are deeply infiltrated by lymphocytes which overgrow the glands and tunica propria and obliterate them. The deeper parts of the mucous membrane show throughout marked dilatation of bloodvessels and lymphatics which are frequently filled by coagulated lymph. The massive lymphoid-cell infiltration of the deeper portions of the mucous membrane obscures the glandular elements of these parts and the muscularis mucosa is indistinct, but the mucous membrane shows nowhere any fibrous or even young fibroplastic tissue. However, the submucous coat presents marked thickening by well-developed fibrous tissue. Within this occurs narrow or broad streaks and aggregates of small lymphoid cells following the course of lymphatics and perivascular spaces. These show here also marked dilatation. In the deeper portions of the submucous coat the connective tissue assumes a hyaline, diffuse appearance. The underlying inner circular muscular coat shows marked hypertrophy. Within this musculature occur streaks and sometimes irregular large areas of inflammatory cell infiltration taking their origin apparently from lymph and tissue spaces. These assume gradually sufficient dimensions to replace patches of musculature. The most recent smaller streaks and areas are made up of cells which are mostly of lymphoid character. The older patches are avascular, fibrillar and cellular granulation tissue, poorly nourished and somewhat necrotic. Thus the muscular coat is interrupted and intersected throughout by these patchy granulomatous-cell infiltrations and loose scar tissue. A somewhat similar but less extensive state of affairs exists in the outer longitudinal muscular coat and the adjoining serosa seems to be involved in places, but only little and very interruptedly.

The enlarged glands which accompanied the specimen showed only inflammatory hyperplasia and lymph stasis.

To recapitulate and sum up:

Neither case is a cancer or a tumor. Both cases represent apparently closely related inflammatory changes within the stomach wall. These appear in the first case of more recent and active character than in the second case. Throughout they carry the distinguishing feature of a granulomatous inflammation, which, in the second, has proceeded to much greater cicatrization. In both the submucous coat suffers more severely and generally, while the first shows a characteristic endarterial involvement of the bloodvessels. In both cases occurs engorgement of bloodvessels and evidence of lymph stasis; in both the muscular coat is hypertrophied, and this is much more pronounced in the second and older case than in the first. This latter also shows an extension of the granulomatous process to the circular layer of the musculature. Finally, in both the serosa shows only slight and irregular involvement.

In regard to the genesis of the lesion:

In both cases, particularly in the first and more recent one, the impression prevails that the involvement of the glandular part of the mucous membrane is a secondary occurrence. On the other hand the lesion becomes manifest earliest in the submucous coat and the lymphoid element of the mucous membrane and extends through and around lymphatics and perivascular spaces, to play most actively in the submucosa. The localized superficial necrosis of glandular parts of the mucous membrane, therefore, is in all probability not an essential element of the lesion. The hypertrophy of the musculature seems also to follow and to depend upon the changes in the submucous coat, a view strengthened by the fact that the more recent first case showed much less of it than the second more advanced one. Furthermore, the granulomatous involvement of the muscular coat which occurred in the second and advanced case also impresses one as following the changes in the submucosa.

From the foregoing it would appear that the cause of this peculiar granulomatous gastritis must be sought in an infection which reaches the stomach through and progresses within lymphatic channels. It is difficult to determine whether the infective agent gains entrance through the lymphoid elements of the mucous membrane or invades in the opposite direction from the outside. If one examines carefully the anatomical and histological findings of these and other cases from the literature it seems that both channels of infection are possible. It is interesting to recall in this connection that in one of our cases a liver cirrhosis was demonstrable at operation. After the infection has once reached the stomach and the lesion made its appearance the evidence in these and other cases indicates that it may remain localized to the pyloric region or may spread to involve more or less the whole of the stomach.

How much lymph and blood stasis are contributory is open to question. These cases cannot be explained on this basis alone.

In regard to the etiology:

It is of course not possible to make any definite statement from these findings, particularly as our knowledge regarding other anatomical conditions in the body is very incomplete. That the features were those of a granulomatous inflammation has already been recorded as well as the marked vascular changes in the submucosa of Case I. This is certainly suggestive of a specific inflammatory process, but whether tuberculous or luetic must remain uncertain. The evidence was not sufficient to establish this with certainty in either case and contributory evidence from other parts of the body was lacking.

As regards the name of the lesion:

Of the many names suggested that of "linitis plastica" is certainly most objectionable. The word "linum" and the phrase "rete ex lino factum" can, with the best stretch of imagination, only be

regarded as a description of the physical appearance of this lesion. The ending "-itis" attached to a name expresses an inflammation. The suffix "-itis" attached to linum therefore makes perfect nonsense.

The objection that the lesion does not represent a gastritis in the strict sense of the term can hardly be regarded as valid, inasmuch as sooner or later practically all the coats of the stomach, including the glandular elements of the mucous membrane, are involved and the mucous membrane may in certain cases possibly even be the port of entrance.

It seems, therefore, that the terminology which has been adopted at the beginning of this report or shortly after "cirrhosis of the stomach" expresses best the general anatomical character of the lesion.

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### SYPHILITIC AORTITIS AND ITS EARLY RECOGNITION.\*

BY GEORGE E. BROWN, M.D.,

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THE first anatomical studies of syphilis of the aorta were made by Morgagni in the middle of the seventeenth century. Later studies by Dohle, in 1888, and Marchand, in 1903, did much to arouse interest in this condition, though the proof they offered as to its etiology was not convincing. They described the pathological changes as a mesaortitis and were impressed with the frequency with which these pathological changes in the aorta were associated with evidences of syphilis elsewhere in the body, and presented the view that the aortitic changes were luetic. It was not until the work of Benda, Wright and Richardson that the absolute proof was found and the successful staining of the spirochetes in the arterial wall supplied the missing etiological link. The further application of the Wassermann test and roentgen rays have greatly increased the interest in this highly important condition. In searching the literature on syphilitic aortitis one is impressed with the paucity of information regarding this disease in the text-books, and attention is paid only to the terminal lesions as aneurysm and aortic valvulitis. I can advise one to read Dieulafoy's<sup>1</sup> classical pictures of aortitis, as it is the acme of clinical conciseness. If one wishes to pursue the subject more thoroughly, Allbutt's works<sup>2</sup> should be studied, as they are the most exhaustive in the English language. It would seem that specific aortitis occupies the same position in present medical literature as tuberculosis did thirty years ago, and only the full-blown cases are deemed worthy of note. More attention must be paid to incipient aortitis, as the only hope of cure lies in the diagnosis before gross changes have taken place in the arterial wall.

\* Read before the Montana State Medical Association, July 10, 1918.

**FREQUENCY.** Statistics on the frequency of luetic aortitis are scanty, but enough work has been done to show that this type of aortitis is very common when diagnosed on the autopsy table but rare when reviewing clinical reports. This discrepancy may be explained in several ways: (1) that aortitis is often a latent manifestation of syphilis; (2) that signs and symptoms of its presence are either lacking or else so insignificant as to be entirely overlooked; (3) that the medical profession has not given this condition sufficient attention and careful examination of the aorta is slighted or else entirely ignored.

There is some excuse for this in view of the fact that the accumulated knowledge on this subject is found only in medical journals and barely mentioned or else ignored in medical text-books. An idea of the frequency of specific aortitis may be gained from Gruber's<sup>4</sup> statistics of 6000 autopsy records, showing aortic lues in 4 per cent. Marchand<sup>5</sup> in a report on 256 autopsies on bodies with acquired syphilis found aortitic lues in 82 per cent. Marchand states there is no doubt many cases of aortic syphilis are mild invasions and subside without doing much damage. Stadler<sup>6</sup> found syphilis of the aorta in 82 per cent. in 156 cases of syphilis. Obendorfer<sup>7</sup> found in 1436 autopsies on adult bodies that 7 per cent. showed aortic lues and in 40 of these the diagnosis was made by the autopsy findings.

The frequency of the association of specific aortitis and tabes and paresis is a well-known observation. Goldscheider<sup>8</sup> in 136 cases of syphilitic aortitis found tabes in 29—other investigations show aortitis in 30 to 40 per cent. of all cases of tabes and general paresis.

In the routine use of the Wassermann reaction in our office I have found 7 cases of specific aortitis in 136 positive Wassermann or luetin tests, 5.1 per cent. This may be low as no doubt some of our cases of positive Wassermans in latent syphilis may have been cases of specific aortitis—in which we were not able to make a diagnosis.

**PATHOLOGY.** Microscopic. Syphilis, as shown by Heller, is an inflammation, with reparative reaction, thus differing with atheroma with its atrophy and decay. The spirochete shows its ravages in all three coats of the arterial wall, the invasion taking place through the vasa vasorum. The adventitia is attacked first, then the media, and these coats bear the brunt of the damage. Collections of lymphoid and plasma cells are found and occasionally giant cells; these occlude the vasa, with resulting weakening of the middle coat. This yielding of the media shows itself later as saccules, bulgings and aneurysms. The cellular collections may show as nodular masses on the intimal surface. These nodules are miliary gummata, showing a tendency to become necrotic in their centers; this, with later absorption, explain the scars and arterial distortions seen in advanced cases. The spirochetes are found with difficulty in the media. Warthin's<sup>9</sup> work has shown that the spirochete is found

in cardiac and aortitic syphilis much more frequently than hitherto suspected.

The gross lesions are easily understood in the light of the microscopic changes. Irregular folds and roughenings of the intima—translucent and pearly plaques. These cushions or wheals may be yellow in color. The distinction between atheromatous deposits and luetic changes is found in the absence of fat and calcareous deposits. The two conditions are frequently coincident. Syphilis usually attacks the aorta at its orifice, and when the extension is toward the heart the valves and coronaries usually suffer, with disastrous consequences to this organ. However, the extension may be from the heart, and in this group of cases the damage is usually less severe. No portion of the thoracic aorta is exempt. Rarely is the abdominal aorta invaded. The gross pathological picture includes the characteristic wrinkling of the intima—longitudinal rugæ, thinned out and scarred areas. The more advanced stages are shown by small saccules and aneurysms.

Studies of luetic aortitis have given rise to the important question as to why the thoracic aorta should bear the brunt and why the abdominal aorta should escape the spirochetic ravages. This important point has been elucidated by the anatomical researches of Klotz,<sup>9</sup> who has shown that this selective action of the spirochete is due to the rich lymphatic supply of the ascending and transverse portion of the aorta, which by their proximity to the abundant mediastinal lymph glands are invariably infected by retrograde movements of the spirochete. This explanation, no doubt, explains the arterial localizations, but it does not tell us why the spirochete should show a preference for the thoracic lymph glands rather than for the abdominal glandular areas.

Syphilis of the aorta exhibits several types and different localizations, and a working classification of these types is made by Dieulafoy, who makes the following divisions:

1. When the disease is confined to the first portion of the aorta. Suprasigmoid aortitis.

2. Syphilis of the aortic valves with incompetence.

3. Aneurysmal forms.

4. Obliteration of the coronary vessels.

I will not attempt to deal with all these types but will try and justify this paper by discussing only the first type, and that in its early form. We are all familiar with syphilitic aortic incompetency and the aneurysmal types, but I am sure none of us are sufficiently acquainted with the earlier forms of luetic aortitis in which the disease has not advanced to a stage where the gross changes are easily detected and where careful cardiac examination shows no aortic valve lesion. This is the type that is easily missed and where the chance of effective therapy is considerable. I have had seven cases of this type of aortitis which I have been able to diagnose as specific

and will try and show how easy it is to overlook this important clinical condition unless one has it continually in mind when examining any obscure chest case. The symptoms are extremely indefinite and are not clear cut, often not severe enough to alarm the patient, but from the fact that chest symptoms in general are associated in the mind of the laity with tuberculosis, often brings these patients to our offices, with a request for a chest examination. The symptoms of specific aortitis are:

1. Pain. Most frequent symptom. Characteristics:

(a) Origin under the sternum, usually at the junction of 1 to 2 portions; or

(b) Sense of constriction or compression. This may vary from a feeling of tightness or pressure to the more severe anginal forms; or

(c) Radiation into the brachial plexus, with the characteristic arm localization—usually of the left side, rarely of the right side and very rarely both sides.

The etiology of aortitis pain is not definitely settled, but probably due according to Allbutt to the inflammation and irritation of the adventitial coat, which has been shown by Dogrel to have special nerve endings in the connective tissues of the pericardial and adventitial coats of the aorta. Aortitis pain is similar to that in fibrous tissues in general, as acute pleurisy, gout, etc.

2. Indefinite Symptoms:

(a) Fatigue. These patients usually are weak, neurasthenic in their complaints, somewhat similar to the group of early tuberculosis; they tire easily. Mental fatigue may be prominent; memory disturbances and headaches are complained of.

(b) Dyspnea. This is an important symptom, present in all of my cases. It varies from a mild dyspnea of effort to the more severe types of strident respiration, as in Case III. This symptom, if not associated with pressure signs, is often due to early cardiac insufficiency, which may be luetic.

(c) Hoarseness. This is usually associated with pressure of the recurrent laryngeal nerve. In Case III the paralysis was permanent, as was the hoarseness. Pressure on the bronchi may cause respiratory stenosis.

(d) Fever. May be present in certain cases. Usually irregular in type. Case IV showed this symptom.

(e) Cough. May be present. This is usually dry and unproductive in type.

(f) Cyanosis. This is observed in some cases—usually due to pressure on the upper vena cavæ. None of the cases in my series showed this sign. Two cases showed a complexion similar to that seen in chronic nephritis; pale with moderate cachexia.

In the early stages of luetic aortitis any one or more of these symptoms may be present. Usually the symptoms are not clear-cut and not severe. It is easy to understand how the diagnosis of incipi-



ent tuberculosis is made in some of these cases. Two of my series had been diagnosed as pulmonary tuberculosis, one of whom spent four months in a sanitarium. Slight, irregular fever; chest pains, indefinite in type, often diagnosed as pleuritic; hoarseness; dry cough; comprised a group of symptoms that could easily be confused with early tuberculosis.

*Signs.* The signs found in aortitis are of considerable value and upon which the diagnosis is made with certainty. The normal aorta of a young adult man should measure 5 to 7 cm. in the transverse diameter. At the age of fifty years, 8 cm. Somewhat less in women. In aortitis the aorta is enlarged in both diameters. We depend on the alterations in width and contour to make our diagnosis. This change may be detected by percussion, and this should be done as a routine in every chest examination, from without inward, in the second and third interspaces. An increased aortic width will be detected in many cases. There is a group of cases, however, in which no percussion changes will be noted. The roentgen diagnosis is by far the most satisfactory method for demonstrating changes in the aortic arch. The roentgen rays show that specific aortitis may show either one or more of the following changes in the normal aortic curve:

1. Enlargement of the aortic shadow to the right. This is usually the earliest demonstrable change, as this is the portion of the aorta first involved in the syphilitic process.
2. Enlargement to the left, with obliteration of the normal aortic knob.
3. Enlargement both to right and left. Increased density of the aortic shadow is suggestive, as is also reduction of the aortic pulsation when viewed fluoroscopically.

The other signs are of doubtful value and I have had no experience with the majority of them. I may mention a few:

- (a) Palpation of the aorta in the jugular notch.
- (b) Elevation of the subclavian artery.
- (c) Undue mobility of the apex, due to elongation of the aorta.
- (d) Changes in the aortic second sound, resembling an Algerian drum, described by Potain as *bruit de tabourka*—a clanging second sound.

Blood-pressure is not elevated, as a rule, or only moderately elevated. This is of some value in ruling out the aortic dilatation of hypertension cases.

The aorta should be examined both fluoroscopically and with plates. The plates should be taken in the upright position and at a distance of from six to seven feet. These seven-foot plates give an accurate size of the heart and aortic shadow. The other important diagnostic finding in luetic aortitis is the presence of a positive Wassermann test—about 75 per cent. of specific aortitis cases show a positive Wassermann reaction and a certain percentage of the

balance will show a typical luetin test. The presence of a positive Wassermann reaction in the absence of any signs of syphilis should direct our attention to the aorta, and in many cases an early aortitis will either be found or suspected and treatment instituted early enough to forestall the more grave sequelæ which are sure to follow. Warthin<sup>8</sup> has shown that the spirochete may be present in the heart, aorta, pancreas and other organs for years without signs or symptoms of their presence. His findings no doubt explain many cases of so-called latent syphilis, with positive Wassermann reactions.

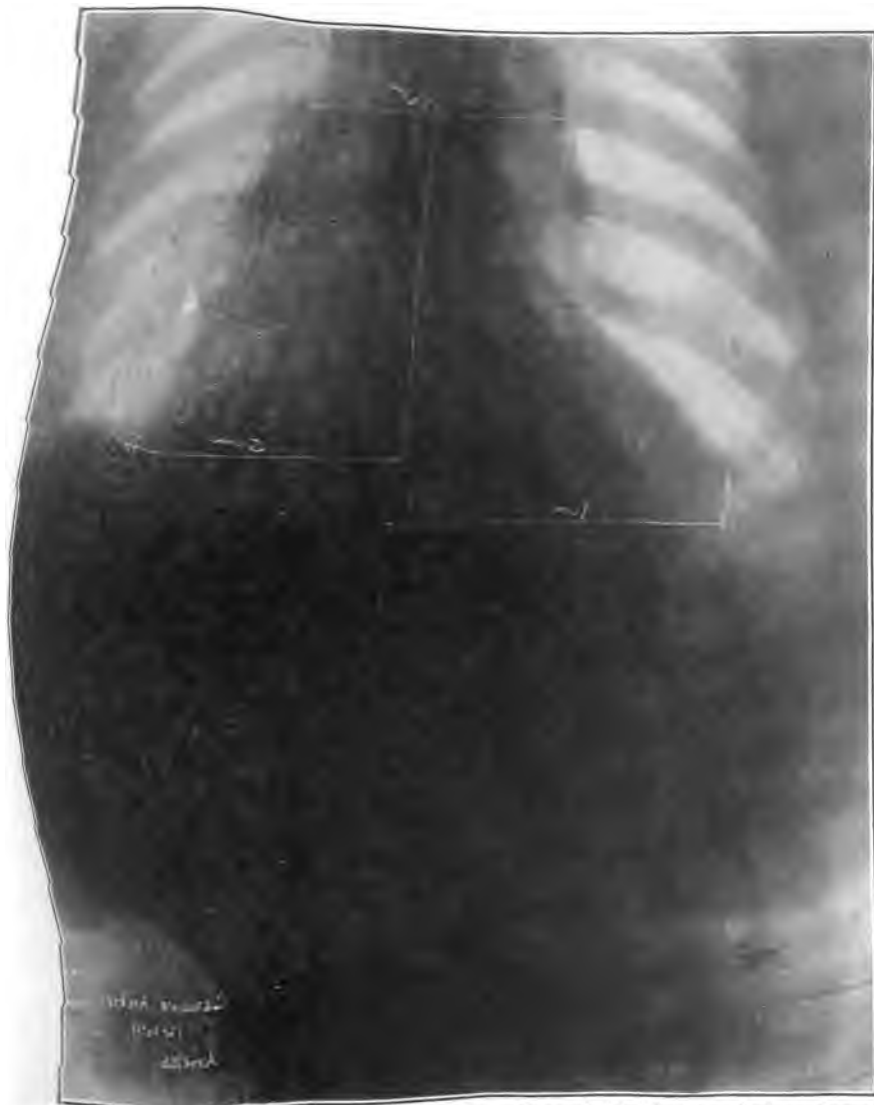
The final important corroborative evidence is the therapeutic test, and when a group of symptoms clear up under a course of mercury and iodides or an injection of salvarsan a suspicious case becomes a diagnostic certainty and treatment is instituted with the assurance of a permanent improvement or perhaps a cure.

**TREATMENT.** Treatment, however, may be very unsatisfactory and too much reliance should not be placed on this test. Many of the symptoms will disappear or improve. Pain usually responds to treatment, though not invariably. In all of my cases with pain the response was satisfactory and assisted in making the diagnosis. In Case IV this treatment response aided materially, as the signs were slight and diagnosis was doubtful. No diminution in the size of the aorta need be looked for or expected. Checking further progression of the disease is the most to be expected. The therapeutic expectations are better in these early aortitis cases, however, than in the more severe invasions. In aortic valvulitis the prognosis is bad. In my group of cases the treatment has been symptomatically satisfactory. The ultimate outcome will depend on much longer observation.

**CASE I.**—Woman, aged fifty-five years. Consulted Dr. Hempstead for hoarseness. She had been diagnosed as an advanced case of tuberculosis by several Eastern men. She gave a history of chronic leg sores, loss of weight, chronic hoarseness, chronic cough and substernal tightness on exertion. Sputum examinations negative. Lungs negative. Aortic arch enlarged to the left. Heart negative. Wassermann 4 plus. After three months' treatment with Hg. and iodides all symptoms were relieved, with a gain in weight of 20 pounds. Three years later still well, having gained 34 pounds in weight, with absolutely no chest symptoms whatsoever.

**CASE II.**—Man, aged fifty-nine years. Comes for bladder trouble. History of luetic infection seven years ago. No treatment. Examination revealed a well-developed case of tabes. Chest examination showed a dilated aorta, especially to the right. No aortic knob present. Heart showed considerable hypertrophy to the left; "horizontal heart." Aortic first sound replaced by a systolic rumble—a suspicious tracheal tug present. Five months later had a very severe anginal attack, the pain radiating to the right shoulder. Irregular weak pulse. Patient died three months later with double

**pyonephrosis.** Autopsy findings: Large hypertrophied heart. No valve lesions. Aorta large and bulging; no aneurysm. Intima showed linear folds and yellow plaques; wall of aorta very thin in



**FIG. 1.**—Case I. Seven-foot heart plate. Note slight dilatation first portion of aorta and marked in descending portion.

portions. Microscopic examination showed typical picture of moderately early specific aortitis. The lymphoid cells show the characteristic grouping about the bloodvessels in the media.

CASE III.—Man, aged forty-seven years. Comes for hoarseness. He gives a suspicious history of exposure to syphilis twenty-five years ago. Had two and a half years' internal treatment. Ten years ago noticed shortness of breath on exertion and hoarseness. In 1914 had a moderate hemoptysis and was diagnosed as tuberculosis. Was under observation four months, during which time he had no temperature and gave a negative response to the von Pirquet and Morro tests. In 1916 had another attack of hemoptysis and

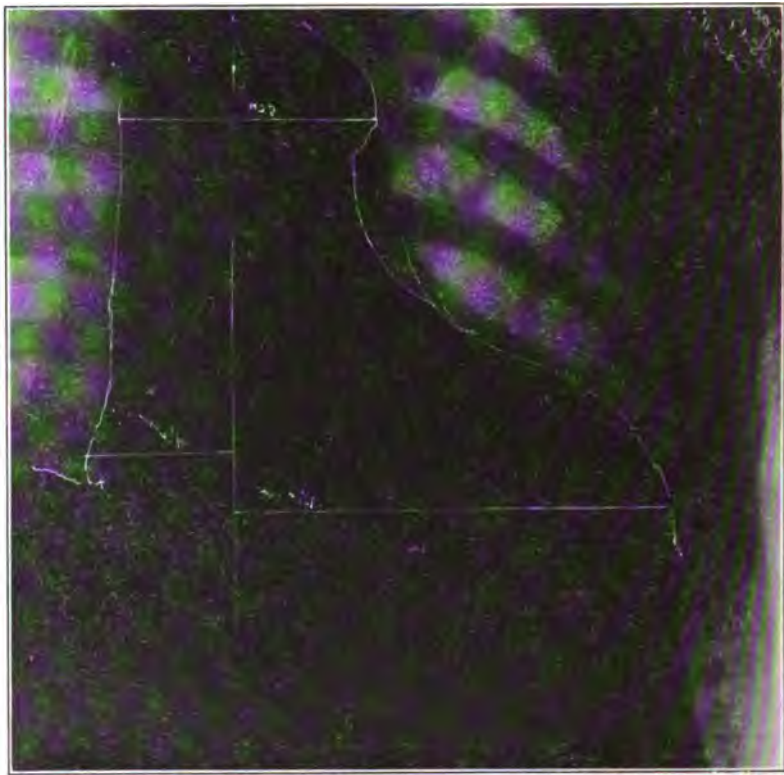


FIG. 2.—Case II. Seven-foot heart plate. Note horizontal heart; dilatation ascending aorta and descending portions. Autopsy showed dilatation most marked in ascending aorta.

was advised to go to a sanitarium, and was told he had evidences of pulmonary tuberculosis, though he did not cough; had no fever and twenty to thirty sputum examinations were negative. Was discharged in four months as an arrested case. Examination by Dr. Hempstead showed complete left-cord paralysis; no inflammatory reaction. Stereoscopic plates of lungs negative, though a moderately enlarged aortic arch found in a seven-foot heart plate; 7 cm. in broadest diameter. Heart sounds negative. Wassermann test

negative. Lutein showed a fairly typical positive reaction. This case had no substernal pain nor distress, but showed a constant dyspnea and attacks of difficult breathing. A diagnosis of specific aortitis was made. He is still under treatment, and the response has not been marked insofar as the dyspnea and hoarseness are concerned; but the paralysis is, no doubt, due to a permanent degenerative lesion of the recurrent nerve. Not much improvement was expected. His general condition has shown considerable improvement.



FIG. 3.—Case III. Seven-foot heart plate. Note heart not enlarged. Dilatation and distention; ascending aorta. This case had recurrent nerve paralysis. No aneurysm.

CASE IV.—Woman, aged thirty years. Comes to the office with a previous diagnosis of pneumonia or pleurisy. She gave the history of having had an attack of substernal “tightness” on exertion; pain radiating to the left. Precordial pain on exertion. No cough. Intermittent fever and chilly sensations, marked weakness and some dyspnea. Lung examination negative. Heart not enlarged. Aortic

first sound replaced by rough murmur, transmitted to neck. Stereoscopic chest plates showed lungs negative but an increase of right hilus shadow. No enlargement of the aorta. von Pirquet test negative. Wassermann 4 plus. No history of syphilis obtainable, but it was subsequently learned that her husband had been under treatment for lues within the past year. Diagnosis: syphilitic mediastinitis and aortitis. One dose of salvarsan cleared up all



FIG. 4.—Case IV. Seven-foot heart plate. Note no change demonstrable in aorta. Probably aortitis of less than two years' duration.

symptoms and the first aortic sound was audible on subsequent examination. This case is undoubtedly an acute syphilitic aortitis and the negative findings as regarding the aortic shadow are easily understood.

CASE V.—Man, aged thirty-four years. Patient had a specific infection four years previously. Took about 5000 Hg. pills during the course of three years. Three months ago commenced having substernal pain. Worse on exertion. Describes it as a dull burning

sensation. Relieved by large doses of potassium iodides. He was also given three doses of neosalvarsan. He was relieved for three years. He returned last month with a recurrence of chest symptoms, and also stating that while exerting himself he had a terrible precordial pain as if a knife were thrust into the heart. He thought he was going to die; this lasted a few minutes. He still has a precordial

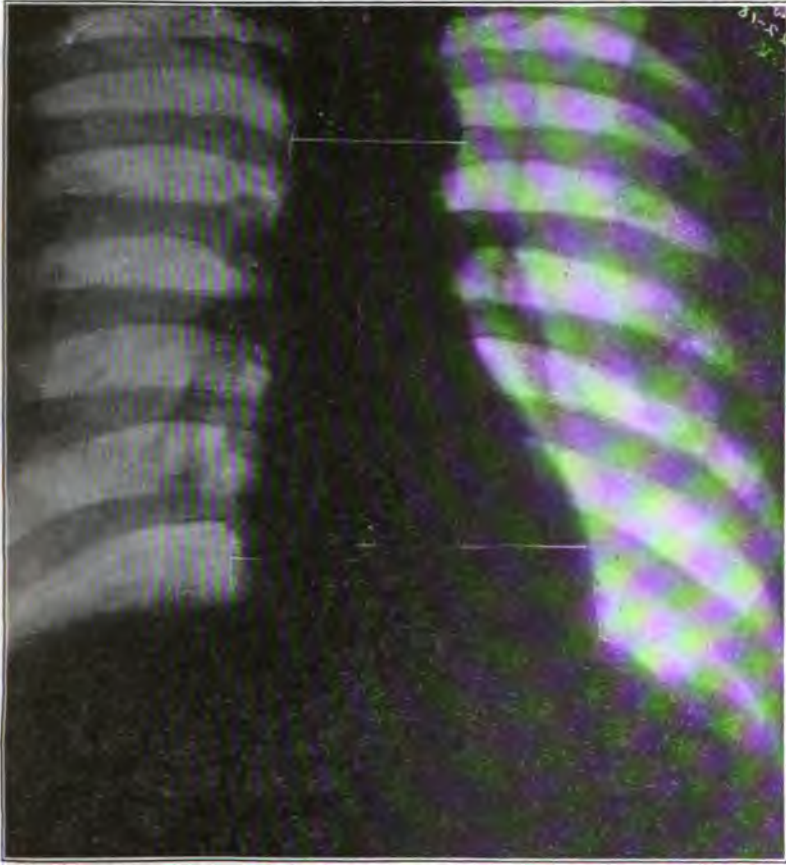


FIG. 5.—Case V. Three-foot heart plate. No change demonstrable in aorta, except slight dilatation of ascending aorta.

soreness. Examination: Head and lungs negative. Heart negative. No enlargement; sounds not abnormal. Seven-foot heart plate shows slight aortic enlargement. Wassermann negative. Lutein test not done, as patient could not remain in town. Diagnosis: Luetic aortitis.

CASE VI.—Man, aged fifty-seven years. No history of infection. For the past three years has had indefinite chest pains, worse on

exertion; localization not definite. Several examinations negative; no diagnosis made. Patient described these pains as tight and constricting in type and aggravated by exertion. Past few months have become substernal; would come on in attacks. For the past three weeks has been incapacitated; weakness, dyspnea, and pain were more pronounced. No fever; pulse, negative. Blood-pressure  $\frac{150}{85}$ . Small obese man. No cyanosis. Some dyspnea. Reflexes

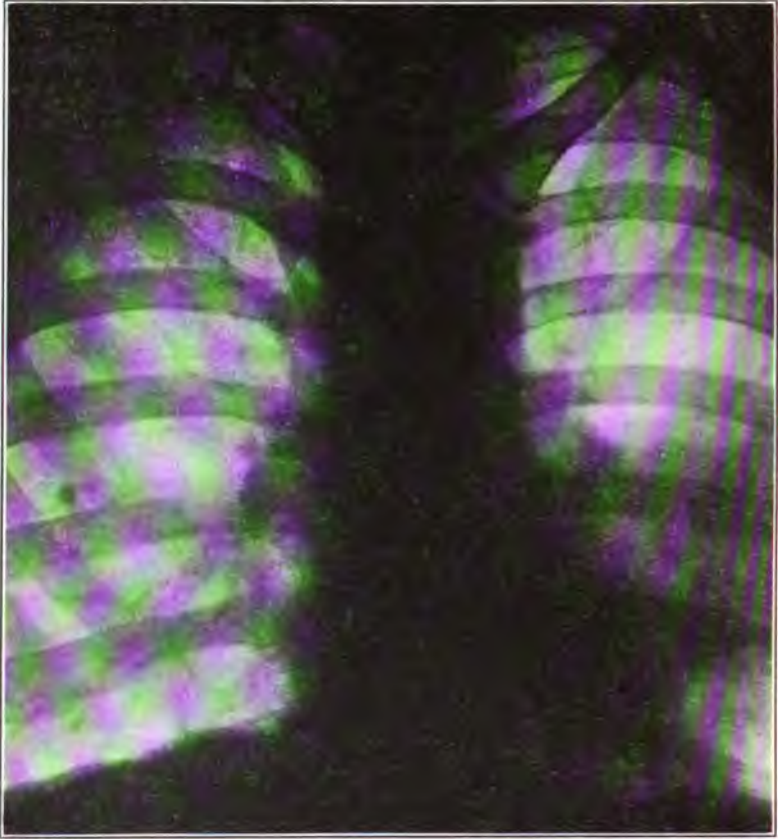


FIG. 6.—Case VI. Three-foot heart plate. No change in aorta. Heart normal size.

normal. Lungs normal. Heart shows systolic aortic murmur. Second aortic loud. Some enlargement to the left. Fluoroscopic examination showed enlargement of arch to right. Irregular contour. Urine negative. Wassermann 4 plus. Patient then admitted a chronic ulceration palmer lesion of three years' duration. Two weeks' treatment with mercury and iodides gave symptomatic relief and he has remained under treatment the past year, with entire relief.



CASE VII.—Man, aged forty-six years. Had primary lesion seven years ago. Treated one year. For the past three years has been going down hill, losing weight. Weakness and obscure chest pains. An examination one year ago was negative, with the exception of a strong positive Wassermann. No treatment was instituted. He again reported to the office several weeks ago, complaining of attacks of dyspnea, precordial pain and substernal distress, with mild pains radiating to both shoulders. No constricting pains. Main complaint is weakness, inability to work and presents the picture of a general breakdown. Examination: Small, haggard looking man; some pallor, general physical examination negative. Heart not enlarged. Aortic first sound impure; second aortic not increased. Stereoscopic lung plates negative; arch not increased in width. Liver not enlarged. Urine negative. Blood-pressure  $\frac{100}{80}$ . Hg. 85 per cent. Talquist. Diagnosis made of luetic aortitis in spite of negative findings regarding demonstrable changes in the arch. Treatment response was speedy and satisfactory.

RESUMÉ OF CASES. I realize that absolute statements regarding the diagnosis of all these cases cannot be made, as the changes in the aortic contour were not always present. I feel, however, that the diagnosis is justified, with the presence of substernal pain, positive Wassermann and treatment response. I believe these are early amenable cases—the type we should suspect and treat accordingly. In Case IV the probable duration of time from infection to onset of symptoms is hard to estimate, but probably not over two years. This time interval may vary from a few months, as in Brooks's<sup>9</sup> cases, where syphilitic aortitis developed during the reseola, to twenty to thirty years. The longest interval in our cases was twenty-five years and the shortest was less than two years.

CONCLUSIONS. Analysis of these 5 cases show several important points:

1. The frequency with which specific aortitis is confused with pulmonary disease.
2. That specific aortitis is not always a late syphilitic manifestation, as note in Case IV probably six to eight months after infection.
3. That practically all physical signs may be absent and the diagnosis will rest on substernal distress, a positive Wassermann test and the therapeutic test.
4. That a positive Wassermann reaction means syphilis, and even in the absence of all outward manifestations of syphilis the aorta should be suspected and active treatment instituted.
5. That a negative Wassermann test does not rule out specific aortitis and a luetin test should be performed and the effect of treatment should be studied.
6. That aortitis should be diagnosed before the more gross pathological changes have taken place, as when that stage is reached usually treatment is ineffective.

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## ADENOCARCINOMA OF THE INTESTINE OF UNUSUAL GENERALIZATION AND WITH PECULIAR CYSTIC METASTASES.<sup>1</sup>

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THE following case is recorded because of the unusual generalization and appearance of the metastases in the intestinal tract, which had some resemblance to pneumatosis cystoides intestini or intestinal gaseous cysts of swine and man and also on account of the difficulty of exactly locating the primary lesion.

**CASE HISTORY.** The patient, a Chinaman, worked in a laundry and was well up to four months ago. He smokes opium to excess but does not use alcohol. Ten weeks ago he had a Neisser infection.

The present condition began about four months ago with indefinite pains in his left shoulder, abdomen, back and upper part of the thighs. Later the pain settled in the lumbar region and his abdomen began to swell. For two weeks before admission to the hospital he had a severe cough and expectorated a large amount of dirty, grayish sputum. He states that warm food agrees with him but that cold food causes pain in his stomach. Without medicine his bowels move only every third or fourth day.

<sup>1</sup> Under a grant of the Cooper Fund of Medical Research in McGill University.

On admission, December 18, 1917, pulse was 96, temperature 97° F. and respirations 18. He lies in dorsal decubitus with his knees flexed and has an anxious expression. Conjunctivæ and mucous membranes distinctly icteroid, skin dry and harsh, with very little subcutaneous tissue, and he has evidently lost weight. Examination of the respiratory system showed only harsh, vesicular breathing, with fine crackles over both the interscapular regions.

*Cardiovascular System.* Negative.

*Genito-urinary System.* No evidence of Neisser; frequency D 4-5  
N. 1.

*Urinalysis.* Amber; turbid; alkaline; specific gravity, 1024. No sugar or albumin; phosphates, carbonates and a few pus cells.

The abdomen is distended and tense, with slight tenderness around the umbilicus. The flanks bulge and are dull on percussion. On palpation an irregular mass can be felt lying transversely across the abdomen above the level of the umbilicus.

December 20 a laparotomy was done and about 1000 c.c. of straw-colored fluid were removed and a specimen was sent for examination. The intestines were found to be studded with nodules and the omentum was rolled up in a mass above the umbilicus. An enlarged, firm gland was removed for examination and the abdomen closed. (This gland was reported as being a metastasis of an adenocarcinoma. See below.)

Following the operation the patient rallied well at first, but later generalized jaundice appeared and he gradually lost weight and died January 21, 1918.

Autopsy was performed four hours after death: The skin shows a deep icteroid tint, the abdomen is markedly distended and contains a large amount of bile-stained fluid. The omentum is thickened, rolled up and extends transversely across the abdomen from the left upper quadrant to the right flank just below the level of the umbilicus. It is studded with numerous small, firm nodules and the lower border consists of a solid, irregular mass of growth. The liver is small, weighing 1280 gm.; the capsule is somewhat thickened and irregularly opaque. On section the cut surface is a dark olive-green color, with indistinct markings. There are several small areas which are yellow and apparently necrotic, with many small, dilated bile ducts in them. There is a stone about the size of a small walnut in the hepatic duct near the gall-bladder. The surrounding tissue is firm, white and partly fibrous. The hepatic ducts are markedly distended. There is a small nodular growth near the cystic duct the size of a small marble. A small pea-sized stone was found in the ampulla of Vater and the gall-bladder was filled with a milky mucoid fluid.

The alimentary tract is particularly interesting. The esophagus is free, the stomach shows several healed ulcers varying in size from a few millimeters to 3 cm. in diameter. Throughout the

intestine, however, there are numerous larger and smaller, sometimes solid, sometimes cystic tumor masses. These can be roughly divided into three classes:

1. Firm, nodular growths, which occur most frequently and are usually situated near or in the mesenteric attachment. They apparently lie immediately beneath the serous coat and appear as round masses with a flattened surface and varying in size from a few millimeters to 1 cm. or more. On section they are small solid masses of whitish-yellow tissue, occasionally with slight honeycombed appearance. Larger, irregular masses occur which seem to be of the same nature and possibly a fusion of several of these nodules. Such a mass occurs in the cecum near the ileocecal valve and in total bulk about the size of a small egg.

2. Beneath the mucous surface of the intestine small spherical masses can be seen which are soft to the touch and cystic, and also vary in size from a few millimeters to over 1 cm. On section they are filled with a thick mucoid material.

3. Several large cysts, projecting into the lumen of the gut, which appear to lie between the serosa and mucosa and covered only by these coats. They are of a bluish color, soft, fluctuating, appear and feel like large emphysematous bullæ and are filled with a whitish, partly gelatinous, partly mucoid material. One of these is situated 57 cm. from the duodenal-jejunal flexure and is about the size of a sparrow egg, and from it sections were taken. Another, slightly smaller, was cut out without being opened and from it Dr. Bruère kindly made a bacteriological report. The largest cyst is situated in the dependent part of the cecum and corresponds in appearance to that already described, but is as big as an egg. In the transverse colon there is another slightly smaller but similar cyst.

The microscopic report on the snipping removed from the omental mass during the exploratory laparotomy on December 19 is as follows:

The sections show a fatty reticular tissue which has been invaded by an adenocarcinomatous growth, which is made up of larger and smaller cystically dilated acini. The smaller and apparently younger acini show a small lumen, a well-formed columnar epithelium sitting on a basement membrane and oval, deeply chromatic nuclei situated near the base. The largest alveoli are filled with a faintly staining, mucoid material. The lining epithelium is, for the most part, missing, or where present is of a low cuboidal type. Between these two extremes intermediate stages can be traced and in many of these glands the epithelium is evidently actively secreting a mucinous material. The tissue also shows a more or less generalized infiltration, with inflammatory cells, mostly of the polymorphonuclear type.

**DIAGNOSIS.** Metastases of an adenocarcinoma in omental tissue. Sections taken at autopsy from several of the nodules grouped above in Class I show a very uniform picture. The growth is most marked in the serosa, and, as in the case of the omental metastases, is made up of glandular loops, which show varying degrees of cystic dilatation, with progressive destruction of the lining columnar epithelium. The musculature has been invaded and destroyed, leaving only an occasional thin strand of muscle cells and the alveolar structures extend into the submucosa. The slight honeycombed appearance seen grossly is due to the largest of the dilated acini, which are of such a size as to be just visible to the naked eye. The mucous membrane is well defined from the growth, but is very thin and represented by irregular villous projections. The individual cells are in a rather advanced stage of necrosis and atrophy, evidently due to lack of nutrition and pressure.

In Class II the microscopic appearance is somewhat different. The metastatic cells evidently reached the submucosa and there found a suitable soil to grow on. The serosa and muscular coats are here intact and form the outer coats of the cystic mass. Immediately to the inner side of the musculature there is a cystic cavity which is filled with mucoid material. The epithelium has completely disappeared and the wall is formed by connective tissue. Between this cystic space and the mucous membrane the edematous remains of the submucosa can be seen, and in it are a few small, irregular, glandular loops. The mucosa itself is similar to that described in Class I.

The third series of sections are taken from the large emphysematous cysts. The cavity is the size of an egg and the wall is very thin, the contained mucoid material giving it a bluish appearance grossly. The cavity lies between the mucosa and the musculature, its inner surface devoid of epithelium and formed externally by the smooth musculature of the gut wall and the serosa and toward the lumen of the gut by fibrillar connective tissue covered by the remaining necrotic and atrophic mucous membrane.

One of these cysts was excised and examined bacteriologically, and Dr. Bruère isolated (1) a variant of *Bacillus communis*, which fermented lactose very slowly and feebly to acid and gas; (2) *Bacillus coli communis*, excretal type.

From the gross and microscopic examination it is evident that the lesion is a widespread metastasis from an adenocarcinomatous growth. The cell type, manner of growth and the character of its secretion all point to its derivation from the intestinal tract, but at the time of autopsy it had become so widespread and so uniform, except for the cystic changes, that the primary growth could not be identified. The metastases in the serosa are most typically adenomatous and, due to the greater resistance of the musculature and connective tissue, the cystic dilatation is well controlled; but

when the metastases reach the loose submucous tissue colloid or mucoid degeneration and distention are the marked feature and typically shown in the group of nodules in Class II. When we come to the four large cysts, which due to their unusual appearance led to this investigation, they are evidently an exaggeration of the mucoid degeneration seen in the second group, with complete destruction of the mucoid secreting epithelium. This can be pretty safely assumed because of the similarity of the cystic contents and the location of the lesion in the submucous coat.

Whether or not the cysts became infected with the gas-forming bacteria long enough before death to partly account for their large size it is impossible to say, but not unlikely. Therefore it appears that these large cysts which grossly were at first thought to be an independent lesion are only a peculiar manifestation of degenerative processes in the original carcinomatous metastases.

The distribution of the metastases is also interesting; they are confined to the gut, peritoneal glands, omentum and the hilus of the liver indicating a dissemination through the peritoneal lymphatics and in this way resembling some cases of tuberculosis.

I wish to express my thanks to Professor Oertel for his kind criticism.

### **THE VALUE OF VENTRICULAR PUNCTURE FOR THE EARLY DIAGNOSIS AND SERUM TREATMENT OF POSTERIOR BASILAR MENINGITIS.**

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THE results obtained about a year ago in the treatment of two babies suffering from posterior basilar meningitis who were admitted to the Willard Parker Hospital are of sufficient interest to justify a short discussion of certain features of the disease and a detailed presentation of the clinical and laboratory reports of the cases. In the literature several late cases of posterior basilar meningitis are reported who recovered after ventricular punctures and injections of antimeningitis serum. No particular attention seems, however, to have been drawn in any of the communications to the importance of an early diagnosis before the progressive character of the symptoms had established the diagnosis beyond a doubt, at which time more or less damage to the brain tissue had already taken place.

The difficulty of recognizing the disease in its early stages, the late complication of an internal hydrocephalus and the resulting high

mortality point to the necessity of utilizing all the available early and often slight symptoms, so as to establish an accurate diagnosis and institute prompt serum treatment by means of ventricular puncture. In antimeningitis serum we have an excellent specific remedy for meningococcus meningitis; it must, however, be injected if it is to be fully efficient in the early stages of the disease and into those places where it will be most active.

The pathological anatomy of posterior basilar meningitis shows that the disease is characterized by a yellow fibrinopurulent exudate which fills up the cisterna magna, spreads downward for a variable distance along the posterior aspect of the cord and forward along the base of the brain so far as the interpeduncular space, the optic chiasm and the tips of the temporosphenoidal lobes.

The early symptoms of the disease in infants below six months of age are not very definite and the diagnosis is often difficult to establish. The only symptoms present may be fine tremors of the extremities, temperature 100° to 104° F., and, of special importance, a slight bulging of the anterior fontanelle. The bulging of the fontanelle in an infant who is quiet and breathing regularly should arouse suspicion and lead to a diagnostic lumbar puncture, especially if one or more of the other symptoms are also present. The results of lumbar puncture in cases of posterior basilar meningitis, in which there is generally an exudate covering and closing the foramina of Magendie and Luschka, may be significant in one of several ways: The lumbar puncture may yield (a) a dry tap, (b) a few drops of clear sterile spinal fluid or (c) 1 to 2 c.c. of purulent fluid. This pus represents some of the material which had formed and settled down in the lower part of the spinal canal before the openings between the fourth ventricle and subarachnoid space in the spinal cord became closed by inflammatory exudate. The diagnosis is readily established in the last group of cases by examining the purulent spinal fluid. Very little of this fluid can be withdrawn, however, and little if any of the antimeningitis serum injected. The indications then become very definite for a ventricular puncture, the removal of a larger amount of fluid and the reinjection of a suitable amount of serum.

In the group of cases, however, that show clinically a slight bulging anterior fontanelle, but give a dry tap or a few drops of sterile spinal fluid on lumbar puncture, the diagnosis remains in doubt. We might hesitate before proceeding to the somewhat more radical procedure of a ventricular puncture. It would be, however, a mistake to wait for the development of the more marked symptoms of a progressive meningitis, such as opisthotonos, retraction of the head and internal hydrocephalus. These symptoms represent more extensive and often irreparable damage to the brain tissue. In the presence of a bulging fontanelle a dry tap in the hands of one who is expert in lumbar punctures, especially if it also follows a second or a third attempt,

should be a clear indication for making a ventricular puncture to establish the necessary diagnosis. A true dry tap can almost always be established by leaving the lumbar puncture needle in place, inserting a second needle into the next space higher up (between the third and fourth lumbar vertebrae) and, after waiting to see if any spinal fluid will escape, allowing some sterile saline to flow into one of these needles. The saline solution will escape through the other needle, showing that both needles have been properly inserted into the subarachnoid space of the spinal canal.

If the case has not been properly treated in the early stages of the disease by ventricular punctures and injections of serum a group of symptoms will gradually develop in the course of the next ten to fourteen days, which are very characteristic but indicate that more or less damage has already taken place. There is an increasing rigidity of the neck, retraction of the head and a moderate or marked opisthotonos. The extremities become extended and spastic, the hands pronated and clenched and the legs adducted and at times crossed. In other cases there may be flexion of the limbs at the various joints. The development of hydrocephalus is indicated by tense and bulging open fontanelles. Dilated pupils, strabismus and sometimes blindness are other symptoms that develop in the later stages. Fever and projectile vomiting are present, and finally death takes place, with progressive emaciation, which is quite a feature of the disease. If the infant should recover from the acute stage of the illness it will, as a rule, develop a permanent hydrocephalus, associated with an impairment of one or more of the sense organs.

In adults cases are occasionally seen that require trephining, ventricular puncture and injection of serum. These patients begin with an ordinary attack of cerebrospinal meningitis and are treated by lumbar punctures daily for possibly a week or ten days. The spinal fluid becomes sterile after the second or third lumbar puncture, but it continues more or less turbid. The clinical symptoms persist and become aggravated. If the patient is conscious he complains of intense headache. There is frequently delirium. The pupils are contracted and the fundi show congested or edematous disks. The explanation for this complication lies probably in the fact that the foramina of Magendie and Luschka have become closed by the plastic exudate over the base of the brain while the space between the spinal cord and the foramen magnum has remained clear. This results in a retention of ventricular fluid containing meningococci and a dilatation of the ventricles of the brain, while the cerebrospinal fluid produced in the subarachnoid space passes freely down into the spinal canal and appears by lumbar puncture. The anti-meningitis serum injected by lumbar puncture can only reach and sterilize the subarachnoid space of the cerebrospinal axis. To reach the ventricles these patients have to be trephined, the lateral ven-



tricles punctured and the serum injected. The puncture and injection of the serum will have to be repeated several times.

In another group of adult cases the patients have gotten over the most acute symptoms and the spinal fluid has begun to clear up distinctly, when there suddenly begins a rapid aggravation of symptoms and the patients complain of intense headache. The eye-grounds show congested or even edematous disks. The spinal fluid is sterile in culture but slightly turbid. If a ventricular puncture is made the fluid is found distinctly less turbid than the spinal fluid and also sterile in culture. In these cases the acute bacteriological infection has stopped both in the ventricles and in the subarachnoid space of the cerebrospinal axis, but the exudate at the base has gradually closed the foramina of exit from the fourth ventricle and the ventricles in the brain are becoming acutely dilated. Repeated ventricular punctures without the injection of serum are indicated in the treatment of these cases. These punctures are made, according to the method of Kocher, through a small trephine opening 2.5 cm. from the median line and 3 cm. in front of the coronal suture. The needle is passed inward and slightly backward for a distance of about 4 or 5 cm., when the lateral ventricle will be reached.

The differential diagnosis in infants must take into consideration the following diseases:

- (a) Tubercular meningitis and the different forms of septic meningitis.
- (b) Meningismus.
- (c) Pneumonia.
- (d) Poliomyelitis and polioencephalitis.
- (e) Meningeal hemorrhage.

**DIAGNOSIS.** The diagnosis is established by lumbar puncture and the examination of the spinal fluid. If there is a dry tap and the patient shows a bulging fontanelle a ventricular puncture is indicated. In adults the persistence or aggravation of the clinical symptoms and a cloudy but sterile spinal fluid indicate a ventricular puncture.

**PROGNOSIS.** The prognosis depends to a great extent upon the stage of the disease in which the diagnosis is established and the serum injected into the ventricles. One of the two cases reported in this communication was treated for three weeks with small injections of antimeningitis serum into the spinal canal. The ventricular fluid obtained from the infant at the end of this time showed a great many meningococci, indicating that the spinal injections of the serum had had very little if any effect on the course of the disease. Three ventricular injections of antimeningitis serum, given at intervals of twenty-four hours, produced a sterile fluid, but the disease had progressed too far and the patient finally died, with marked emaciation. The second patient was treated in the early stages of the disease and recovered completely. The prognosis would seem to

depend therefore, to a considerable extent, upon the time when the diagnosis is made and proper treatment instituted.

**TREATMENT.** The treatment consists of puncture, daily or every other day, of the lateral ventricles, withdrawal of the fluid and reinjection of a suitable amount of antimeningitis serum. The interval between each puncture and the total number of punctures will depend upon the clinical course and the examination of the ventricular fluid. From four to six punctures and injections of serum may be required. The amount of fluid withdrawn from the ventricles varies from 20 to 50 c.c. and the amount of serum injected from 15 to 35 c.c. The treatments are not discontinued as soon as the ventricular fluid is found sterile on culture, but one or two additional serum injections should be given. Cases of meningococcus meningitis are occasionally observed that are not treated sufficiently with serum and subsequently show relapses, as indicated by an increased temperature and reappearance of positive meningococcus cultures in the spinal fluid, even though the latter had for a few days been negative in cultures.

The technic of ventricular puncture is simple but requires certain precautions. The infant should be wrapped in a sheet and placed in the dorsal position, with the head brought near the edge of the table. The area over and around the anterior fontanelle is shaved, if necessary, and sterilized with tincture of iodine. One assistant holds the head of the infant firmly between his hands and another one secures its body. The operator sits at the head of the table. The lumbar puncture needle used in this operation should preferably be not larger than a No. 18 gauge, three inches long and have a short bevelled point (George Tiemann & Co.). The needle is introduced through the anterior fontanelle on a horizontal line connecting the two lateral angles, 1 cm. from the middle line, in order to avoid injuring the longitudinal sinus. It is passed to a depth of from 2 to 5 cm., when the lateral ventricle will be readily reached. The direction of the needle from its insertion through the scalp is almost perpendicular but slightly outward and forward. The needle is held very gently and supported, rather than firmly fixed, between the fingers. The plunger in the needle is removed and the ventricular fluid allowed to escape into a test tube, which is held by an assistant. If the fluid flows out too rapidly its escape may be temporarily stopped by partly reintroducing the plunger into the needle. The small size of the needle will avoid too rapid a removal of the ventricular fluid and injection of serum as well as unnecessary trauma of the brain tissue. After withdrawing the fluid from the ventricle a gravity outfit, consisting of the barrel of a 10 to 20 c.c. syringe and connecting rubber tubing, is attached by an assistant to the needle and the antimeningitis serum, previously warmed to body temperature, is slowly injected. Care should be taken to reinject less fluid than is removed. At the end of the operation the needle is

gently withdrawn and a sterile dressing applied. It is not necessary or advisable to wash out the ventricle with salt solution before the injection of the serum. For repeating the injection it is preferable to use the other ventricle. Each specimen of fluid withdrawn is carefully examined by smears and bacteriological cultures.

The infant should be kept in the hospital under observation for at least four weeks after convalescence has set in. Before discharging the patient a lumbar puncture should be made to see whether a clear spinal fluid can be obtained. This would indicate the reestablishment of the communication through the foramina of Magendie and Luschka between the ventricular cavities in the brain and the subarachnoid space in the spinal canal.

Every effort should be made to have the breast feeding continued during the patient's stay in the hospital. This is an important feature of the treatment, as changing to bottle feeding is likely to greatly diminish the chances of the infant's recovery. After the patient has been discharged from the hospital, observations should be continued for a period of several years to determine any possible impairment of the mentality or of any of the special sense organs.

The following are the records of the two cases treated at the Willard Parker Hospital. The contrast in the final results, due to the institution of proper treatment at different stages of the disease, illustrates quite definitely the necessity of early ventricular puncture for diagnosis and treatment.

CASE I.—Frank S. (Chart I). Patient, aged two and a half months, was admitted to the hospital on May 9, 1917. Had been ill for eighteen days previous to admission. The patient presented the typical clinical picture of an advanced basilar meningitis. There was marked retraction of the head, opisthotonos, spasm of the limbs and bulging of the anterior fontanelle. The patient was first seen at home by a physician connected with the meningitis division of the Department of Health. A lumbar puncture was made but it resulted in a dry tap. Two other punctures were made at subsequent visits, but each time only a few drops of sterile bloody fluid were obtained. After admission to the hospital on May 9 (nineteenth day of disease) four more lumbar punctures were made, which again only resulted in a few drops of sterile spinal fluid. At each lumbar puncture a few cubic centimeters of antimeningitis serum were injected intraspinally.

The patient showed no clinical improvement during this time. His condition became rapidly worse; the opisthotonos was more marked, the anterior fontanelle showed greater bulging and the child was becoming progressively more emaciated.

May 15 (twenty-fifth day of disease). First ventricular puncture was made; 45 c.c. turbid fluid obtained, containing numerous meningococci in smears and cultures; 20 c.c. antimeningitis serum injected by gravity.

May 16 (twenty-sixth day of disease). Anterior fontanelle bulging. Second ventricular puncture; 45 c.c. turbid fluid withdrawn, showing several colonies in culture; 20 c.c. antimeningitis serum reinjected.

May 17 (twenty-seventh day of disease). Third ventricular puncture; 40 c.c. slightly cloudy fluid withdrawn, which showed only one colony in culture; 18 c.c. antimeningitis serum reinjected.

May 18 (twenty-eighth day of disease). Fourth ventricular puncture; 10 c.c. slightly cloudy fluid obtained, which was sterile in culture. No serum injected.

May 20 (thirtieth day of disease). Fifth ventricular puncture; 30 c.c. almost clear fluid obtained, which was sterile in culture; 20 c.c. antimeningitis serum reinjected by gravity.

May 21 (thirty-first day of disease). Patient died. Toward the end the patient showed marked marasmus.

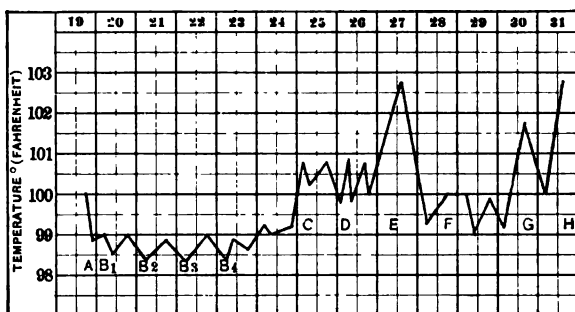


CHART I.—Frank S. (Case I). A, lumbar puncture; 15 c.c. blood-tinged fluid withdrawn; B1, lumbar puncture; few drops of blood-tinged fluid withdrawn; B2, lumbar puncture; few drops of blood-tinged fluid withdrawn; B3, lumbar puncture; few drops of blood-tinged fluid withdrawn; C, first ventricular puncture; 45 c.c. of turbid fluid withdrawn; 20 c.c. serum; D, second ventricular puncture; 45 c.c. of turbid fluid withdrawn; 20 c.c. serum; E, third ventricular puncture; 40 c.c. of slightly turbid fluid withdrawn; 18 c.c. serum; F, fourth ventricular puncture; 10 c.c. of slightly turbid fluid withdrawn; G, fifth ventricular puncture, 30 c.c. almost clear fluid withdrawn; 20 c.c. serum; H, patient died.

CASE II.—Giulietta M. (Chart II). Two and a half months old. Admitted to the hospital May 13, 1917. Ill for three days before admission. Symptoms slight and not characteristic. Temperature,  $100^{\circ}$  F.; occasional tremors of upper and lower extremities; slight but distinct bulging of anterior fontanelle even when the baby was quiet. No rigidity of neck or Kernig's sign. On day of admission a lumbar puncture gave 2 c.c. of purulent fluid containing numerous meningococci in smears and cultures. Several other lumbar punctures were made on the same day and on the following morning but no more spinal fluid could be withdrawn nor could the antimeningitis serum be injected into the spinal canal; 20 c.c. of serum were therefore given subcutaneously on the day of admission.

May 14 (fourth day of disease). First ventricular puncture; 15 c.c. of cloudy fluid withdrawn, which showed numerous meningococci in smears and culture; 10 c.c. serum reinjected.

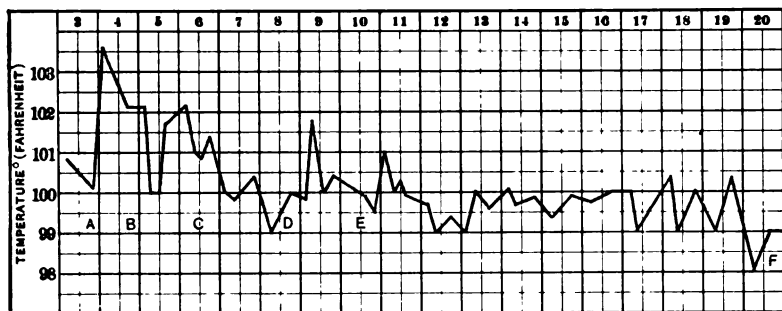


CHART II.—Giulietta M. (Case II). *A*, lumbar puncture; 2 c.c. purulent fluid, containing meningococci; 20 c.c. antimeningitis serum given subcutaneously; *B*, first ventricular puncture; 15 c.c. of turbid fluid withdrawn; 15 c.c. serum injected; *C*, second ventricular puncture; 20 c.c. of turbid fluid withdrawn; 10 c.c. serum injected; *D*, third ventricular puncture; 40 c.c. of turbid fluid withdrawn; 15 c.c. serum injected; *E*, fourth ventricular puncture; 40 c.c. of slightly turbid fluid withdrawn; 20 c.c. serum injected; *F*, lumbar puncture; 10 c.c. of clear spinal fluid, sterile in culture.



FIG. 3.—Giulietta M., three months after the attack.

May 16 (sixth day of disease). Anterior fontanelle bulging; second ventricular puncture made; 20 c.c. turbid fluid obtained, showing a smaller number of meningococci in smears and culture; 10 c.c. serum reinjected.

May 18 (eighth day of disease). Third ventricular puncture; 40 c.c. slightly turbid fluid obtained, sterile in culture; 15 c.c. serum reinjected.

May 20 (tenth day of disease). Fourth ventricular puncture; 40 c.c. slightly turbid fluid withdrawn, which was sterile in culture; 20 c.c. serum reinjected.

May 31 (twenty-first day of disease). Lumbar puncture; 10 c.c. clear spinal fluid obtained, which was sterile in culture. Patient discharged from the hospital.

During the course of the disease the patient developed a slight retraction of the head, which was hardly noticeable, however, at the time of discharge from the institution. The breast feeding was continued during the entire time. It is interesting to note that a nasal culture made on May 16 (sixth day of disease) showed the presence of meningococci.

Fig. 3 was taken three months after the patient was discharged from the hospital. The examination at that time showed that the baby was apparently normal and had made a complete recovery.

A second reëxamination of the patient was recently made (one year after the attack) and the baby was found to be apparently normal and to have made the usual progress in its mental and physical development.

**SUMMARY AND CONCLUSIONS.** 1. A prompt ventricular puncture is indicated in cases that show progressive meningeal symptoms and give a dry tap on lumbar puncture. In some patients the lumbar puncture may show a few drops of purulent spinal fluid, but a sufficient amount cannot be withdrawn, even by aspiration, with a syringe, and little or no antimeningitis serum can be injected.

2. Even less pronounced meningeal symptoms, such as slight but definite bulging of the anterior fontanelle, tremors of the extremities and fever should lead to a ventricular puncture in cases that have given repeated dry taps in the hands of an experienced operator. Such early ventricular punctures are of vital importance in the successful treatment of cases of posterior basilar meningitis.

3. In adults the persistence or aggravation of the clinical symptoms, associated with a persistently cloudy spinal fluid, which has become sterile after two or three injections of antimeningitis serum, indicate in many cases the necessity for a ventricular puncture. In these patients the lumbar puncture may show a sufficient amount of spinal fluid, but the outlet from the ventricles is closed off and the serum injected into the spinal canal does not reach these infected regions.

4. Ventricular punctures should be repeated daily or every other

day; 20 to 50 c.c. of fluid are withdrawn and 15 to 30 c.c. of serum injected by gravity. The serum should be warmed to body temperature and a smaller amount always reinjected than the amount of fluid withdrawn. Three assistants are generally necessary to carry out the operation carefully and safely.

5. The interval of time between the punctures and the total number of punctures will depend upon the rapidity in the reaccumulation of the fluid, as indicated clinically by the reappearance of a bulging anterior fontanelle and upon the result of the bacteriological culture of the ventricular fluid.

6. A lumbar puncture should be made at the time the patient is discharged from the hospital in order to determine the reestablishment of the communication between the ventricular cavities in the brain and the subdural space in the spinal canal.

7. If the baby is breast-fed every effort should be made to have the breast feeding continued while the patient remains in the hospital.

8. Occasionally the diagnosis may be assisted in cases giving a dry tap, and before deciding upon a ventricular puncture, by making a culture of the nasal discharge and finding the meningococcus present.

9. Cases of posterior basilar meningitis should be followed up for a period of years to determine the final outcome in those who recover after ventricular punctures and injections of antimeningitis serum.

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### PRIMARY CARCINOMA OF THE GALL-BLADDER: AN ANALYSIS OF TWENTY-THREE PROVED INSTANCES OF THE DISEASE.<sup>1</sup>

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IN the series of 1000 operatively and pathologically demonstrated instances of gall-bladder disease which I reviewed a year

<sup>1</sup> Read at the Twenty-third Annual Meeting of the American Gastro-enterological Association, Atlantic City, N. J., May 6 and 7, 1918.

since,<sup>2</sup> there occurred 31 cases of malignancy (3.1 per cent.). Of these gall-bladders the neoplasm was primary in 23. In the remaining 8 cases the gall-bladder was secondarily invaded by extension of malignancy from adjacent viscera. There occurred no instance of primary neoplasm of the bile ducts. It is thus evident that of a large series, including gall-bladder affections of nearly every type, primary malignancy arose in 2.3 per cent. The practical value of this rate of the incidence of gall-bladder neoplasms is indicated by the observation that it is more than four times the frequency of primary malignancy of the appendix, and that of neoplasms involving the organs concerned with digestion the gall-bladder is involved fifth in frequency (1 of stomach; 2 of colon and cecum; 3 of rectum; 4 of esophagus; 5 of gall-bladder; 6 of liver; 7 of appendix).

It is frequently stated that the diagnosis of primary malignant disease of the gall-bladder is not difficult. This statement holds true for instances in which there is extensive involvement when pronounced general constitutional upset has occurred and in which the prognosis is evident to even a layman. That there are actual difficulties concerned with the accurate diagnosis of primary neoplasm of the gall-bladder is proved by the fact that of the 23 cases in my series in but 7 instances (30.4 per cent.) was the unqualified, prelaparotomy diagnosis correctly made and recorded in the histories and operation cards. In no case in which early well-localized gall-bladder malignancy existed was there a correct preoperative diagnosis. It would seem, consequently, that the clinical diagnosis of curable neoplasm of the gall-bladder occupies a status relatively similar to that of the clinical diagnosis of early curable primary gastric malignancy.

On account of the foregoing observations it is considered that a clinical analysis of the 23 instances of primary gall-bladder malignancy included in my series of established gall-bladder disease will not be altogether valueless.

**SEX.** It is commonly recorded that females are affected approximately three times as frequently with malignant disease of the gall-bladder as are males. (Musser, Zenker, Siegert, Mayo, Moynihan and others.) From this observation it is usually deduced that because the incidence of gall-stones in females is about three times that in the male, gall-stones must of necessity be the cause of gall-bladder neoplasms. In spite of many successful experiments in the production of gall-stones there is no instance on record in which the deliberate experimental production of the calculi nor the accidental arising of such a consequence of foreign body (ligatures, drains, etc.), resulted in malignant disease, and this in spite of the fact that the so-called "irritant" has lain even for years in a pre-

<sup>2</sup> Smithies, Frank: Proceedings of the Section in Medicine, American Medical Association, New York Session, June 7, 1917.



viously healthy or diseased gall-bladder. (Homans, Jacques, Meyer, Mignot.)

In our series of primary malignancy of the gall-bladder there were 16 males and 7 females.

**AGE.** The average for my series was for both sexes 59 years. The minimum age in males was 44 years, the maximum 76 years (average 57.9 years). In females the minimum age was 56 years and the maximum 72 years (average 62.2 years). It would seem that in spite of the greater prevalence of gall-stones in the female the average age at which malignant disease of the gall-bladder occurs is more than five years later than in the male.

**HEREDITY.** There was only one patient of the series in whom a definite blood relationship of malignancy could be elicited. In another patient the husband had died about a year previously from cancer of the stomach.

**DURATION OF SYMPTOMS.** In the 100 cases of cancer of the gall-bladder which Musser<sup>2</sup> collected from various non-related sources and from the literature in 1889 the average duration of the ailment is stated as six and two-third months, with a minimum duration of seven weeks and a maximum of four years. It is quite evident when one analyzes cases that in numerous instances the patient has been affected with a gall-bladder dyspepsia of two distinctly definite types, viz.: (a) a clinical form, not that commonly considered malignant, and (b) a terminal complaint frequently evidencing such serious local and constitutional disturbances as to render a suspicion of some malignant process highly probable. There were in my series 16 cases (69 per cent.) in which a previously harmless type of gall-bladder dyspepsia had been followed by an alarming complaint. In the early period the ailment was commonly intermittently manifested and extended in the average over 9.6 years (minimum 3 years; maximum 36 years). The terminal phase of the disease was one of continuous malfunction (often, clinically, on the part of the gall-bladder) and in duration averaged 10.3 months (minimum 5 weeks, maximum 3 years).

Of the 7 cases in which from its inception the affection had been of an obstinate and progressive type the duration averaged 3.4 months, (minimum 6 weeks, maximum 6 months).

It would seem that consideration of these two types of dyspepsia ultimately proved to be associated with malignant disease of the gall-bladder might furnish more than a clinical hint relative to the nature of the ailment and might also throw considerable light, etiologically, upon the relationship existing between chronic gall-bladder irritation (infective, chemical, foreign body, *e. g.*, calculi) and gall-bladder irritation. It should be here emphasized that chronicity, histologically speaking, must be differentiated from

<sup>2</sup> Boston Med. and Surg. Jour., December 5, 1889, No. 23, cxxi, 553.

chronicity, indicating months or years' duration of disease: a powerful continuously acting stimulus may be quite capable of producing histological changes of malignancy quite as marked as those occurring when an intermittently acting or weakened agent has been manifest over a long period of time.

**SYMPTOMATOLOGY.** In 17 patients the early history of the affection indicated rare or frequent attacks of such dyspepsia as is commonly associated with catarrhal cholecystitis or cholelithiasis. Not rarely these attacks had borne definite relationship to an acute infectious disease. The history of typhoid fever was obtained from 12 patients—pneumonia from 3 and malaria from 1. At the time of their coming to the hospital, in 20 instances the patients were affected with a continuous and disabling ailment. The characteristics of this ailment now will be considered.

**APPETITE.** In 14 patients (60.8 per cent.) there was persistent anorexia. The food desire was lessened in 5, but well maintained and in nowise abnormal in 4.

**WEIGHT LOSS.** There was but one patient who had maintained normal weight. In this case early exploration to relieve distressing gall-bladder dyspepsia disclosed small sessile papilloma. In the remaining 22 cases of my series, weight loss, generally associated with physical weakness, averaged 28 pounds (minimum 15 pounds, maximum 60 pounds). The weight loss was frequently astonishingly rapid, and of itself when taken in connection with an ailment clinically dependent upon gall-bladder malfunction should have furnished a significant hint relative to the development of neoplasm. In three months one patient lost 40 pounds, another 60 pounds in seven months and a third 28 pounds in five weeks. It was not unusual for persistent weight loss associated with unaccountable anorexia weakness or diarrhea to cause alarm a considerable time before symptoms or signs of gall-bladder anomaly presented. Five patients came for the examination at which malignancy was discovered on account of the persistent and puzzling loss of weight.

**BOWELS.** In 11 cases distressing constipation was recorded; in 4 stools of normal frequency, while 8 patients were subject to diarrhea not rarely uncontrolled by diet and commonly exhausting. Nocturnal diarrhea, with disturbance of sleep and rest, seemed to be an important influence in causing rapid weight loss and cachexia. This was especially noticeable when the gall-bladder malignancy had invaded the pancreas (6 cases).

**STOOLS.** There were no abnormal findings in 8 instances. The stools of the remaining 15 patients persistently or intermittently indicated interference with free bile flow. They were definitely acholic in 9 cases.

**BILE PIGMENT IN THE URINE.** Bile pigment in the urine as shown grossly by dark sherry-colored urine, capped with thick green brown or olive froth or by chemical test, was present in 11 instances.

The urine analyses of 5 patients returned report "suspicious" for bile coloring.

(g) JAUNDICE. This was definitely manifested by 14 patients. In 3 patients the jaundice was intermittently present. In 11 patients the jaundice was persistent. In these cases the skin coloration and the sclerotic tinting ranged from lively greenish-brown to a muddy or dusky olive green. Itching of the skin or distressing anal pruritus was obstinate in 7 of the continuously jaundiced patients. Such itching was often of significant importance with respect to loss of sleep and rapidly developing weakness.

(h) FEVER. Although Musser concludes that in malignancy of the gall-bladder the temperature is liable to be subnormal, rise in temperature with or without chilly sensations or sweats was recorded in 5 patients of my series. Its character was similar to that of cachectic processes associated with malignancy in general or with such exhausting ailment as progressive tuberculosis, viz., a subnormal morning temperature with a rise toward evening or upon unwonted physical or mental exertion. The maximum temperature recorded was 102.3°. In one instance of indefinite upper abdominal nodular tumor not associated with jaundice or pain, the character and persistence of the fever led to a preoperative diagnosis of tuberculosis of the peritoneum. In the presence of ascites, such mistake in diagnosis is not easily avoided unless there be careful scrutiny of the patient's history previous to the period of his presenting complaint.

PAIN. Some degree of abdominal discomfort was experienced by 21 patients (91.2 per cent.). There was severe pain in 16 cases (69 per cent.). In 5 cases sharp, prostatic colic-like attacks of pain required opiate relief. In 2 patients the character of the pain suggested gall-bladder perforation.

The abdominal distress was *continuous* in 14 cases but only *intermittently* manifested in 7. It was not unusual to note aggravations of pain, even of colic-like degree, in those patients in whom a continuous abdominal discomfort had been experienced.

*Location of Distress.* Eleven patients complained of general epigastric pain; in 5 discomfort was definitely confined to the right upper abdominal quadrant, in 1 each distress at the right costal arch, the region of the navel and the xiphoid. In 2 instances there was generalized liver region pain, with a point of intensity below the tip of the right scapula.

*Transmission of Pain.* There was persistently referred pain in 14 cases. In the order of frequency, pain transmission occurred to the right back, the right shoulder, the tenth to twelfth dorsal vertebrae and the midepigastrium. Distress at the referred point was not infrequently more annoying than was that experienced at the zone of pain inception.

*Time of Pain.* Maximum distress was commonly recorded as occurring shortly after the taking of food, upon sudden changes of position or after jolting or jarring (*e. g.*, after a rise over a rough road). Only 2 patients complained of severe night pains.

*Relief of Pain.* In 8 instances opiates were required to make the patient comfortable. Fasting, vomiting, free catharsis, gastric lavage or the administration of alkalies were commonly helpful agents.

**ABDOMINAL TENDERNES.** This was recorded in 22 of the 23 cases. It was usually in the right upper quadrant or in the epigastrium generally. In 7 instances the tenderness was so exquisite as to suggest gall-bladder perforation with protective peritonitis.

**ABDOMINAL TUMOR.** Such was definitely determined or indefinitely delimited in 17 cases (74 per cent.). The tumor or ridge commonly occupied the right upper abdomen. In 4 cases it extended well across the epigastrium. In size the tumor ranged from a finger-like ridge to an oval or pear-shaped mass as large as a grapefruit. Its *consistency* was commonly firm, although in 3 instances there was a cystic feel, with a suggestion of fluctuation. Its *surface* was definitely rough or nodular in 9 cases. The tumor was *movable* on respiration or change of position in 4 instances. In the remainder the mass seemed deeply fixed. *Tenderness* over the tumor was noted in 12 patients.

**ENLARGEMENT OF THE LIVER.** Enlargement of the liver occurred in 11 patients (46 per cent.) of the entire series and in 8 cases (47 per cent.), in which abdominal tumor was coincident. In degree the liver enlargement ranged from the organ's being just palpable to its extension downward as much as 5½ inches below the right costal limit. Of the 11 patients in whom the liver was enlarged there was palpable hepatic nodulation in 4. The liver consistency was commonly very firm: in fact, so firm as to suggest the diagnosis of interstitial cirrhosis. Two patients were brought under observation with such previous diagnosis. In 1 case there was concomitant splenic enlargement.

**ASCITES.** This was demonstrated in 3 patients (13 per cent.) before laparotomy. In 2 other patients free abdominal transudate was discovered at operation (ascites 21.7 per cent., for the series). Pressure upon or actual malignant invasion of the portal vein or its radicles commonly produced the ascites. In 1 instance there was involvement of the receptaculum chyli and the thoracic duct with a resultant chylous ascites.

**BELCHING AND NAUSEA.** Belching and nausea were annoying in 17 patients. With these symptoms a distressing sensation of upper abdominal "crowding" or "up pressure," particularly at night or after eating, was sufficiently uncomfortable to prevent adequate feeding or uninterrupted sleep.

**VOMITING.** This occurred either as a daily or an irregular event in 18 patients (79 per cent.). Vomiting of retained food was observed in 10 patients. The vomitus of 13 patients was persistently bile-stained. In 3 cases in which obstruction occurred near the papilla of Vater the vomitus was persistently colored with muddy brown bile. In these cases the gastric extracts grossly suggested those commonly to extensive malignant stenosis of the pyloric end of the stomach.

**TEST-MEALS.** Data is available in 12 cases. Persistent twelve-hour food retention existed in 5 cases. The *average free HCl* was 21 (minimum 4, maximum 56). There were 6 instances of achlorhydria. The *average total acidity* was 30.1 (minimum 4, maximum 64). *Chemical test* for blood pigment was positive in the gastric extracts from 6 patients. *Lactic acid* was recorded in 5 cases.

*Microscopically.* Yeasts were in excess in 5 cases and *sarcines* coincident in 4. Organism of the Boas-Oppler type were present in 3 of the achlorhydria gastric contents where there was associated food stagnation.

**ROENTGEN FINDINGS.** There were 11 cases in which roentgen examination had been made before laparotomy. In 5 cases roentgen-ray plates demonstrated atypical shadows in the gall-bladder zone strongly suspicious for calculi. In 3 cases there was interference with the emptying of the stomach, the barium meal remaining longer than six hours in the gastric cavity. In 1 case there was a filling defect at the outlet of the stomach, which, interpreted in the light of the clinical symptomatology and the test-meal examinations, appeared to result from pyloric cancer. At fluoroscopy, the roentgen examination not rarely proved of service in demonstrating that the palpable abdominal tumor lay outside the stomach or other portions of the alimentary tract. There was 1 instance in which the malignant gall-bladder involved the hepatic flexure of the colon. In this case there was not only a colon filling defect but also marked retardation in the progress of colon contents caudad.

**OPERATIVE FINDINGS.** 1. *The Neoplasm.* In 4 cases the malignant change was well defined and located in the fundus or body of the gall-bladder. In 2 cases there were malignant papillomata. In the remaining 17 cases there was extensive neoplastic involvement of the entire gall-bladder, with contiguous invasion of adjacent viscera.

2. *Histologically* the lesion was constantly carcinoma of the columnar or spheroidal cell type.

3. **CONCOMITANT INCIDENCE OF GALL-STONES.** Of the 23 instances of primary malignancy of the gall-bladder, cholelithiasis was an associate finding in 16 patients (69 per cent.). In the remaining 7 patients it was not possible to prove the previous presence of gall-stones, although in 4 cases the early histories suggested such. The relationship of cholelithiasis to malignant disease has already been commented upon. It would appear that the fact that gall-stones are often found

in malignant gall-bladders furnishes evidence worthy of note with respect to the gall-stones acting as sources of irritation and the production of malignant hyperplasia of the gall-bladder mucosa. It is not impossible, however, that in malignant gall-bladders calculi may form as a consequence of cancerous change altering the excretory function of the gall-bladder mucosa or preventing proper emptying of the viscus. From the clinical histories of many patients who later on are shown to have malignant disease of the gall-bladder, attacks simulating gall-stones can be elicited at a time previous to the more recent ailment which is apparently clinically malignant. It would certainly seem that in patients in whom gall-stones can be proved to exist, from the clinical or special examinations, their early removal, together with the gall-bladder, might be a considerable factor in preventing malignancy in the individual and also in the human family.

4. INVOLVEMENT OF ADJACENT VISCERA. In 11 cases the lymph nodes showed metastases; in 8 cases the liver was extensively invaded; in 6 the pancreas; in 2 the stomach and in 1 case each there was extension to the omentum, the hepatic flexure of the colon and the retroperitoneal lymph tissue.

OPERATIVE PROCEDURE. In 11 patients abdominal exploration only was possible on account of extensive malignancy. In 4 cases cholecystectomy was performed and once posterior gastro-enterostomy for the relief of pyloric obstruction. In the remaining 7 patients the gall-bladder was drained.

RESULT. Two patients recovered and have remained well longer than four years. Fatal termination followed in the remainder either shortly after operation or within eight months subsequent to leaving the hospital.

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## THE RELATION OF PAIN IN GASTRIC AND DUODENAL ULCER TO MUSCULAR ACTIVITY OF THE STOMACH.

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SINCE the discovery by Boldireff of the presence of contractions in the empty stomach and the demonstration by Cannon that these contractions represent the so-called "hunger pangs," the subject of the activity of the fasting stomach has been most thoroughly worked out by Carlson<sup>1</sup> and his associates both for man and animals. The earlier work of Carlson indicated that the sensory evidence of these contractions, carried by way of the vagus

<sup>1</sup> The Control of Hunger in Health and Disease, Chicago, 1916.

system, originated in the contractions themselves, and the suggestion was made that the pain of gastric and duodenal ulcers might originate through this mechanism.

A number of investigations, notably by Ginsburg, Tumpowski and Hamburger<sup>2</sup> and by Carlson,<sup>3</sup> have demonstrated that the pain in a number of cases of peptic ulcer was in fact rhythmic and that the patient's record of his accessions of pain corresponded to the graphic demonstration of typical hunger contractions. The published tracings of these researches are very convincing, but in taking many histories in ulcer cases one is obliged to note that while accessions of pain are sometimes found to have a rhythmic character, often one finds that the story of pain is continuous and that no interruption or rhythmicity can be read into it. Indeed, the only cases which, for one reason or another, we were able to study at the hospital during the winter of 1916-17 were of this character. The results in this short series, therefore, without controverting the findings of others, seem to show that pain in patients suffering from proved, active, gastric and duodenal ulcers is not of necessity associated with any recognizable activity of the gastric walls and that intense gastric activity can occur in these same patients without giving rise to pain.

The method of study was that of Carlson: the use of a soft, thin-walled rubber bag, readily swallowed and connected to a water manometer of great delicacy by a fine, soft rubber tube. The float of the manometer was made to write without the interposition of a lever upon the slow kymograph. The patient indicated painful sensations by an electric signal. Before the work on ulcer patients was undertaken a year's work on dogs and a study of other human cases had made the method thoroughly familiar.

CASE I.—P. B. Surgical 5941. Aged sixty years. Acute gastric ulcer. Symptoms of only twenty days' duration previous to these observations.

*Previous History.* Unimportant. No previous gastro-intestinal symptoms noted.

*Present Illness.* Twenty days before the patient began to have high epigastric pain coming on one-half to one hour after eating. At times the same pain comes at night. It is severe, dull, continuous and felt often as a radiation into the right chest and back. Vomiting, at irregular intervals, of coffee-ground material. No retained food. Slight relief from vomiting, but, on the whole, pain is nearly continuous, with short, slight food relief.

*Physical Examination.* Somewhat emaciated man, drowsy and in pain. Questionable mass in epigastrium.

<sup>2</sup> Contributions to the Physiology of the Stomach XXXV: The Newer Interpretation of Gastric Pain in Ulcer, Jour. Am. Med. Assn., 1916, lxxvii, 990.

<sup>3</sup> The Origin of the Epigastric Pain in Cases of Gastric and Duodenal Ulcer, Am. Jour. Physiol., 1917, xlv, 81.

*Gastric Analysis.* Fasting contents, 50 c.c. Free HCl, 25 c.c. Total acidity, 46 c.c. Test meal: at end of forty minutes: Free HCl, 76 c.c.; total acidity, 44 c.c. At end of eighty minutes: Free HCl, 26 c.c.; total acidity, 40 c.c. At end of 120 minutes: Free HCl, 14 c.c.; total acidity, 34 c.c. Last two specimens bile-stained. Evidently continuous acidity.

*Röntgen Study.* Large smooth defect in posterior gastric wall just below the lesser curvature, half-way from the pylorus to the cardia. No stasis.

*Motility Study I.* December 19, 1916. Sixteen hours after eating. Observation for one and one-half hours. Continuous slight epigastric pain of the kind usual to the patient. Low tonus, with slight variations, but no contractions.

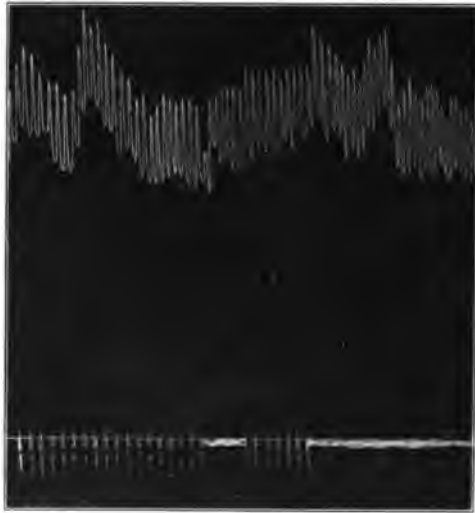


FIG. 1.—Case I. Gastric ulcer. Onset of pain is indicated by cessation of time marker. Digestion peristalsis of low grade is shown. Diminution rather than increase of this peristalsis with onset of pain. Low tonus. Base line should be about 1.5 cm. above time marking line. Five-second marking.

*Motility Study II.* December 20. Two hours after eating. Observation for one and three-quarter hours. Comfortable for three-quarter hour. Moderate gastric tonus with some evidence of short digestive rhythm. Some epigastric pain ushered in by a painful period of about fifteen seconds, followed by a free interval of thirty seconds. After this pain was continuous. No contractions or notable variation in tonus for one hour (Fig. 1). The pain signal was given by interrupting the time-marking apparatus. Base line not indicated. (It should have been about 1.5 cm. above the time line.)

At operation a penetrating ulcer just below the lesser curvature



in the mid-stomach was found. It was adherent to the pancreas, was unhealed and surrounded by a narrow inflammatory zone.

*Summary of Case I.* Acute gastric ulcer. Study made on fasting stomach shows habitual slight pain without contractions. Study made after eating shows severe pain accompanied by low tonus without contractions.

**CASE II.**—W. C. C. Aged twenty-eight years. Surgical 5992. Chronic gastric ulcer. Symptoms of twelve years' duration.

*Previous History.* Unimportant.

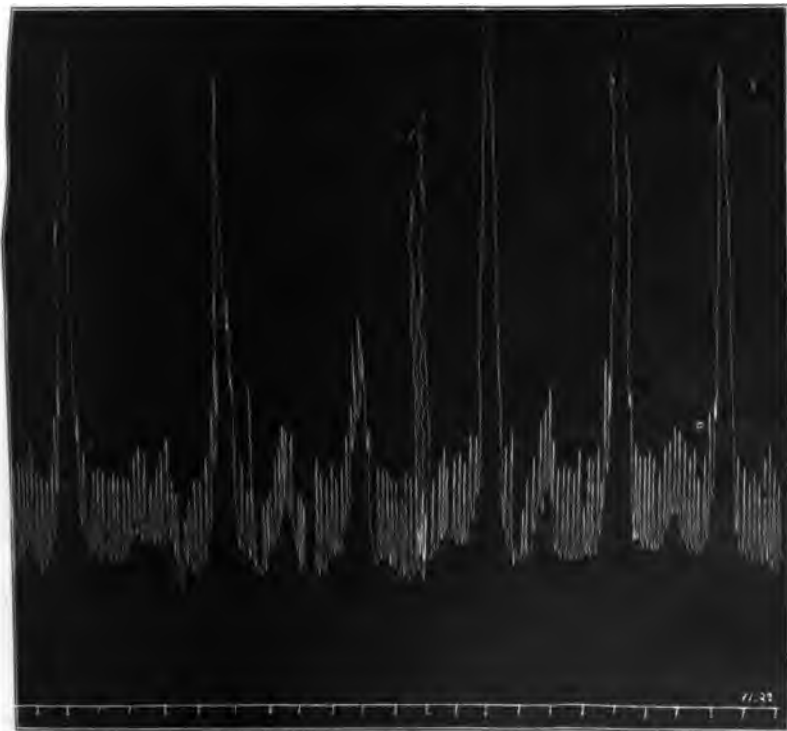


FIG. 2.—Case II. Gastric ulcer. Vigorous hunger contractions (empty stomach) without pain. Oscillation at *x* is due to a cough. Half-minute marking.

*Present Illness.* Beginning twelve years ago, distress and “weakening feeling” coming on after meals, with pain in the lower abdomen coming on early after meals or in one or two hours. Typical remissions (one of eighteen months). For five years, dull, grinding epigastric pain at night. Sour eructations. Relief from vomiting, soda and passing of gas by the rectum. Pain now situated a little above the umbilicus and radiates to sides and back.

*Physical Examination.* Unimportant.

*Gastric Analysis.* Fasting contents: Eight to ten drops, showing free HCl (not titrated), benzidine + + +. Test meal: At the end of forty minutes: Free acid, 29 c.c.; total acidity, 50 c.c. At the end of 120 minutes: Free acid, 54 c.c.; total acidity, 72 c.c. At the end of 160 minutes: Free acid, 60 c.c.; total acidity, 76 c.c. Increasing acidity for nearly three hours after test meal. Continuous acidity.

*Roentgen Study.* Deep niche in lesser curvature. Slightly hypotonic dilated stomach. Pylorus and duodenum negative. Emptying in four hours.

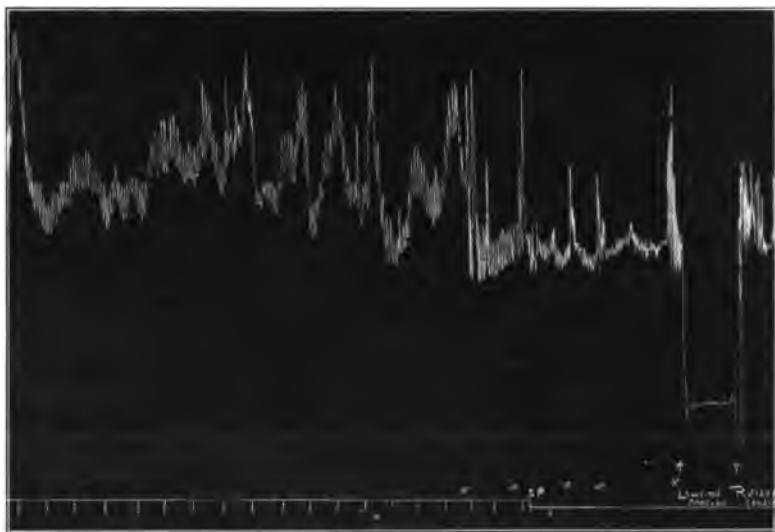


FIG. 3.—Case II. Gastric ulcer. Same day as Fig. 2, but after eating full meal. Note vigorous digestion peristalsis up to point marked *S. P.* Here severe pain suddenly began. At point *x* patient made sudden movements, interrupting otherwise nearly level record. Note diminution of respiratory excursion after onset of pain. Tension of balloon lowered and again raised without altering pain. Half-minute marking.

*Motility Study I.* December 27, 1916. Fourteen hours after eating. Observation for three hours. Typical hunger contractions, of which Fig. 2 gives an adequate idea. They occurred in two periods, were unusually vigorous and were not accompanied by any pain whatsoever nor by any sensation by which the patient could recognize them.

*Motility Study II.* December 27. Same day as the preceding study. Two hours after a hearty meat dinner (12.30 p.m.). Swallowed bag at 2.15 p.m. Observation for three hours. Until 4 p.m., *i. e.*, three hours after eating, tracings showed digestion peristalsis (twenty second rhythm of variable intensity), with fairly high tonus, and no pain was noted. Patient asleep, lying on left side, until

pain began at about 4 p.m. and waked patient up. It was of the usual dull, grinding character and caused the patient to writhe, interrupting diaphragmatic breathing, as shown by the diminished respiratory excursions of the manometer needle. Aside from small oscillations, due to body movements, the indicator recorded no gastric activity. On turning the patient upon his right side, the pain ceased in ten minutes, recurred again for a brief period, and as it disappeared the patient passed gas freely by the rectum and gastric motility returned (Fig. 3).

*Operation.* January 3, 1917. An open penetrating ulcer near the lesser curvature was found. Considerable area of induration about it. Adherent to pancreas. Excision of ulcer. Posterior gastro-jejunostomy.

*Motility Study III.* January 17 (two weeks' after operation). Fourteen hours after eating. Tracings show high tonus, well-marked digestive rhythm (twenty-second contractions), which gradually developed into rather irregular hunger contractions in the course of two hours.

*Summary of Case II.* Chronic gastric ulcer. Powerful gastric contractions in stomach without pain. Pain after eating, coming on during a period of active digestion peristalsis, with cessation of this peristalsis during the painful period. Cessation of pain on turning the patient from the left to the right side, followed by gradual resumption of digestion peristalsis.

**CASE III.**—C. W. S. Aged forty-three years. Surgical 6521. Chronic duodenal ulcer. Symptoms of eighteen years' duration.

*Previous History.* Unimportant.

*Present Illness.* Typical, twice a year, the periods of pain coming on regularly about three hours after eating. Pain in the nature of a severe soreness, as of "something squeezing by raw surface;" it always was felt under the edge of the ribs on the right. Marked night pain. Clean-cut food and soda gave relief.

*Physical Examination.* Unimportant.

*Gastric Analysis.* Fasting contents, 40 c.c.: Free HCl, 60 c.c. Total acidity, 78 c.c. Test meal (three forty-minute periods). On first two periods duodenal contents obtained. (No free HCl.) At the end of the third period 135 c.c. were obtained during the withdrawal of the tube. Free HCl, 70 c.c.; total acidity, 80 c.c. Apparently continuous high acidity.

*Roentgen Study.* Permanent irregularity of the first portion of the duodenum. Hypertonic stomach.

*Motility Study I.* March 31, 1917. Eight hours after eating. After swallowing the bag the patient lay on the right side and the pain began in several short periods, soon becoming continuous. During this time the gastric tonus was low and there were no contractions. When turned on the left side the pain ceased and hunger contractions began. During the period of strong hunger

contractions which followed the patient experienced one painful sensation (Fig. 4) in association with an unusually weak contraction. When turned again upon his right side the contractions ceased and after one or two painful sensations steady pain set in. During the onset and establishment of pain there were no contractions and gastric tonus was very low (Fig. 4).

*Operation.* April 2. Puckered scar in beginning of duodenum. Mucous surface of ulcer not seen. Finney pyloroplasty.

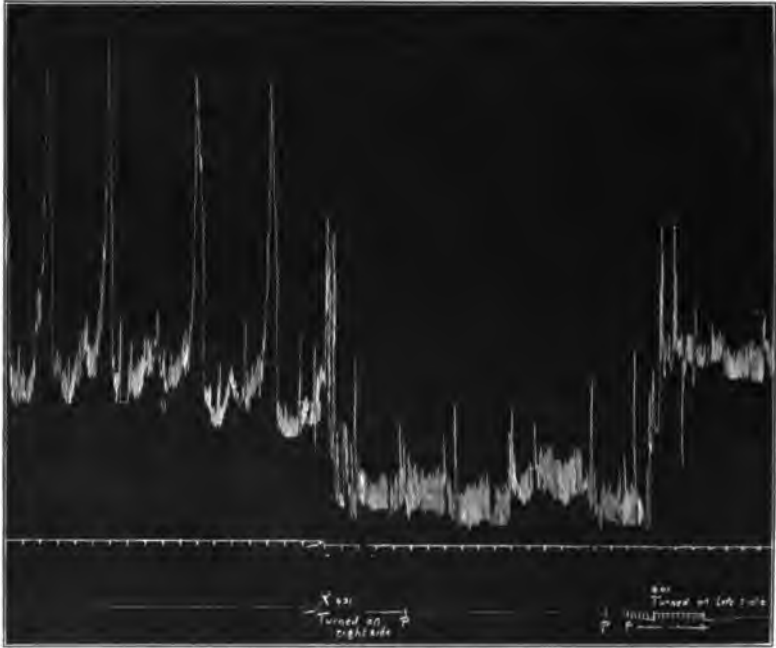


FIG. 4.—Case III. Duodenal ulcer. Fairly vigorous hunger contractions (empty stomach), which ceased on turning patient from left side to right. A moment of pain corresponded to low contraction on left of record. Pain indicated by signal on lower line (and by letter *P*). It became continuous nine minutes after turning upon the right side. Establishment of continuous pain noted by frequently depressing pain signal and then holding it down. Alterations in tension are due to changes in position. No contractions after pain began. Half-minute markings.

*Motility Study II.* April 22. Twenty days after operation. Twelve hours after eating. Two contraction periods seen. First period with the patient lying on his back. The second with the patient lying on his left side. This period ended soon after turning the patient upon the right side, possibly a coincidence, but interesting in connection with the preoperative study (Fig. 5). No sensations noted by the patient.

*Summary of Case III.* Chronic duodenal ulcer. Gastric contractions on fasting stomach without pain. Pain without gastric contractions. Apparent influence of position on pain and contractions.

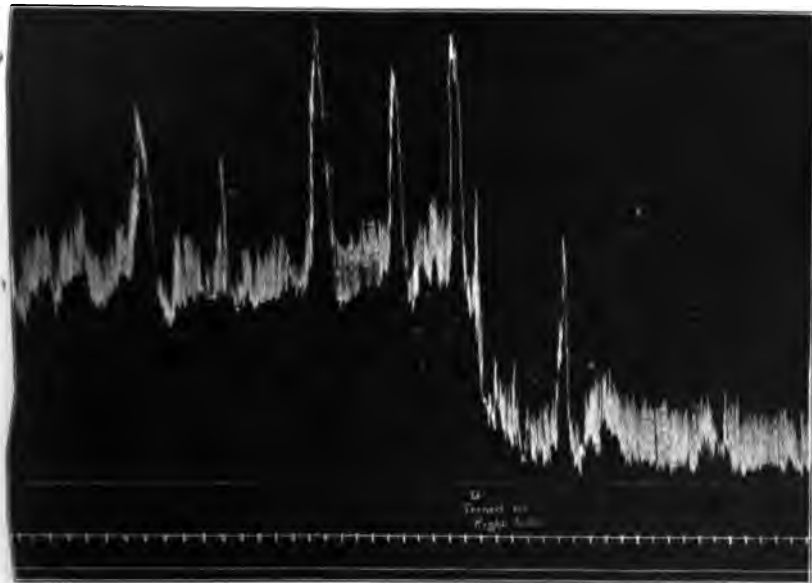


FIG. 5.—Case III. After operation. Short period of hunger contractions on rather high tonus. Cessation of period soon after turning to right side. No pain; clinically well. Compare with Fig. 4. Half-minute markings.

DISCUSSION. Taking up these cases separately, Case I falls into the class of those ulcers which give rise to pain of a continuous nature. Food relief was short and incomplete and was followed by an accession of pain which slowly died down to the previous, dull, continuous level. Such a condition has been classified by Friedman<sup>4</sup> as belonging to a group of cases characterized by adhesions, high acidity and prolonged pyloric spasm. According to Carlson it would again be placed as an instance of pyloric contraction in the presence of ulcer and high acidity. The absence of any recognizable contraction of the fundus would not then interfere with the interpretation of pain as due to excitation of oversensitive pain nerves tortured by active muscular contractions of the pyloric region (which are not recognized in the balloon method of study). One may therefore say there is no evidence in this case which supports the interpretation of pain as being due to muscular activity of the stomach, and, on the other hand, no evidence to oppose this

<sup>4</sup> Time Relations of Gastric Pains, with Special Reference to Gastric Adhesions, *AM. JOUR. MED. SC.* 1916, cli, 735.

hypothesis, since pyloric contraction may, in fact, have taken place, due to the acid reflex from the duodenum.

Case II, however, is difficult to explain under any hypothesis. The patient presented a typical gastric ulcer history, high continuous acidity, some "grinding" pain and on balloon study, typical powerful hunger contractions without a trace of pain. On a full stomach (the same day as that on which the hunger contractions were demonstrated) the pain came on some three hours after eating, waking the patient from a sleep, during which gastric digestion peristalsis had been quite active. As the pain appeared the gastric peristalsis ceased, the tonus was lowered and the effect was conveyed that the onset of pain had diminished gastric activity. The effect of the patient's position in bed (as in Case III) is noteworthy. The pain appeared while the patient lay on his left side, and soon disappeared, without other treatment, upon turning over upon the right side. As the pain disappeared, gastric peristalsis was resumed and tonus increased. Coincident with this relief the patient passed gas by the rectum. One might suppose, therefore, that the position of the abdominal contents, and possibly some drag on a sensitive mesenteric attachment, for which a cause might be found in the posterior penetration of the ulcer, were more concerned with the pain than the gastric activity itself. It is certainly true that intense hunger contractions caused no pain and that pain was coincident, with no demonstrable gastric contractions.

Case III was one of "copy-book" duodenal ulcer; typical pain, food relief and acidity. Again, the pain was absent during active hunger contractions and occurred with the cessation of these contractions. In this case, again, the position of the patient seemed to influence the pain. It began while the patient lay upon his right side (low gastric tonus, no contractions), ceased at once on turning upon the left side (hunger contractions began), and when the patient turned back to the right side the pain soon became continuous (low tonus, no contractions).

The relation of pain to motility of Cases II and III was strikingly alike, though the nature and situation of the pain was quite different, and one might have expected that the lesions would have had some points in common. However, one was a penetrating gastric ulcer adherent to the pancreas and the other was a duodenal ulcer, almost reactionless and unusually free from adhesion of any sort; in fact, the duodenum was so mobile that a Finney pyloroplasty was easily performed. It seemed in Case II (the gastric ulcer) that the obvious involvement of the base of the large intestine must have been concerned with the pain, especially since relief was coincident with the passage of flatus by the rectum. The same mechanism cannot be invoked in the duodenal ulcer.

Carlson suggests that when no gastric contraction is found to coincide with pain that the pain is likely to have originated in

pyloric spasm reflex upon the passage of acid gastric contents into the duodenum. There is nothing in these studies to confirm or disprove such an hypothesis. There is evidence, however, that, even in the presence of an active ulcer far removed from the pylorus, powerful contractions of the fundus may cause no pain, and pain may occur independently of any muscular activity of the fundus.

## **ANATOMIC POINTS DETERMINING THE DIRECTION OF THE NEEDLE AND THE PROPER ROUTE FOR LUMBAR PUNCTURE IN CHILDREN AND ADULTS.**

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UPON consulting the voluminous literature on rachientesis, one is immediately impressed by a certain diversity of opinion as to many of the essential points of the technic. There appears to be in general a tendency to treat lightly the details of the procedure, despite the fact that it is these apparently minor points of technic that are so important in bringing about a successful result. This is more especially the case because lumbar puncture is a "blind" operation and is guided mostly by the sensation of touch, and success depends in no small measure on the correct site of introduction and direction of the needle.

During the 1916 epidemic of poliomyelitis, and subsequent to that time we were privileged to perform or supervise the operation in over 1000 lumbar punctures in all varieties of meningeal conditions, and for both diagnostic and therapeutic purposes. Clinically, we were impressed by certain points relative to the technic which seemed to facilitate the puncture and which rendered dry taps an unusual, indeed almost rare, complication. It is our present purpose to speak of two of these points, one relative to the route for puncture and the other concerning the direction of the needle.

The conclusions ultimately drawn were made first on the living subject and were later confirmed by studies in the dissecting room on the cadaver.

**THE ROUTE FOR PUNCTURE IN CHILDREN.** There exists some divergence of opinion among authors as to the route to be employed in young patients. Most authorities, however, seem to concede that the median route is most advantageous. Anyone who has performed a number of punctures, using the median route, must certainly be impressed by its simplicity in children.

There are several reasons for the superiority of this route over the lateral: The spinous process of the lumbar vertebræ in young

patients are more or less rudimentary. They are short, thick and horizontal, often tipped with cartilage, and they do not overlap (see Figs. 3, 4 and 5). Thus there exists between them an interval which is often quite wide and which permits the introduction of the needle without any liability of touching the spines. (The shape of these interspinous spaces, Quincke<sup>1</sup> appropriately designated as oval or rhombic.) Moreover, the interspinous ligaments at an early age are only slightly developed; in fact, when the needle has pierced the skin and outer layers of the supraspinous ligaments it quickly glides through the remaining tissues and is immediately felt to lie within the dural sac, the distance traversed being very small, as little as 13 mm. in a young infant. By flexion of the spine, which is usually easily attained in young patients, the back is rounded out, the interval between the adjacent spinous processes is widened and the operation is further simplified. It must be remembered, too, that in young children the lumbar region of the back is covered by a very thin layer of subcutaneous and muscular tissue, beneath which the peritoneum is encountered. In lateral puncture it is evidently possible for the novice to miss his mark and penetrate deeply into the tissues of the opposite side of the back, even reaching and passing through the peritoneums and wounding some of the abdominal parietes, especially the kidneys. This is well-nigh impossible by the median route unless great force is used.

The only arguments which can be truthfully made against the median route in children is that in infants especially the room for approach is less than with the lateral route. Nevertheless, the space between the spines is amply wide to allow the passage of even a larger caliber needle without the slightest difficulty.

On several occasions during autopsies on young children and infants we have noticed the character of the vertebræ. At this age they are not distinct and separate bones connected merely by ligamentous attachments as in adults, but, on the contrary they appear *en masse*, partly cartilaginous and united into one piece, from which the individual bones are separated only with the greatest difficulty, and even then incompletely. The spinous processes are very rudimentary straight and largely cartilaginous. The supraspinous ligaments are relatively strong and intimately blended with the cartilaginous spines. As a result of this construction, when a large caliber needle is introduced the elasticity of the entire spine is so great that it allows quite an anterior bending of the supraspinous ligament before the limit of elasticity is reached and the ligament is penetrated. Anyone who has performed many punctures in infants by the median route must have experienced at the initial introduction the same sense of resistance, especially if the needle is not sharp and is of large caliber, which latter requisite is, of course, only essential for serum treatment. This constitutes, of course, a slight disadvantage to median puncture. However, these few argu-



ments against it are greatly offset by its numerous advantages, which are explained later on under the route for puncture in adults. Suffice it to say here that its great simplicity, the certainty of the result, the easy facility with which a beginner acquires the method, the diminished liability of injuring nerve filaments or bloodvessels, the advantages for spinal anesthesia or serum injections are among the points strongly in its favor.

**THE ROUTE FOR PUNCTURE IN ADULTS.** In adults the majority of authors are strongly in favor of the lateral route. Quincke<sup>1</sup> originally recommended introducing the needle a few millimeters laterally because of the strong interspinous ligaments which are often encountered in the median line in robust individuals. Stewart,<sup>2</sup> Starr,<sup>3</sup> Foote,<sup>4</sup> Holmes,<sup>5</sup> Ruhräh and Mayer,<sup>6</sup> Porter,<sup>7</sup> De Ridder,<sup>8</sup> Heiman,<sup>9</sup> Wolf,<sup>10</sup> Holwell,<sup>11</sup> Donitz and Bier, Spear,<sup>12</sup> Duflos<sup>13</sup> and numerous other authorities advise the lateral route. Foote<sup>4</sup> contends that the needle should be started one-half inch to the right or left of the median line, thus avoiding the necessity of forcing it through one inch of supraspinous and interspinous ligaments. Duflos<sup>13</sup> introduced the needle 7 to 8 mm. from the median line and claims that the ligamentum subflava offers only slight resistance, but he admits that these ligaments may become ossified in older persons. De Ridder<sup>8</sup> advises that the needle be started at a point 1.5 cm. outside the midline. Ker<sup>14</sup> resorts to the lateral route only in adults with strong tough interspinous ligaments.

Lavalle,<sup>15</sup> Cabot,<sup>16</sup> Kaplan,<sup>17</sup> Lorenz,<sup>18</sup> Sophian,<sup>19</sup> Neal and Du Bois<sup>20</sup> and Barker<sup>21</sup> are among the very few writers who make use of the median route in adults. Kaplan<sup>17</sup> punctures in the sitting posture, introducing the needle in the median line and straight forward. Sophian,<sup>19</sup> while admitting some of the advantages of the lateral route, claims the median has the great advantage of simplicity and is easily performed even by the inexperienced. Lorenz<sup>18</sup> is strongly in favor of the median line, stating that he employed the lateral route in a large number of punctures in which dry taps frequently occurred, but since he has made use of the median failure to obtain fluid, occurs in less than 2 per cent. of his cases. Lavalle<sup>15</sup> is strongly convinced of the advantages of the median route and mentions Guinard's name as an advocate of the method. Neal and Du Bois,<sup>20</sup> whose experience in meningeal conditions has been unusually extensive, use the median line.

Most authors opposed to median puncture base their main objection on the thickness of the supra- and interspinous ligaments in the adult and on the resistance which they claim these ligaments offer to the passage of the needle. A few object because of the alleged danger of breaking the needle especially in a restless, violent or delirious patient by the sudden extension of the back.

In order to determine the foundation for the objections to the median route as based upon the thickness and resistance of the inter-

spinous ligaments, the author undertook a study of these ligaments postmortem in a small series of three adult cadavers, of thirty-five, forty and forty-eight years, respectively. The dissections were performed on spines which had been disarticulated from the rest of the cadaver, and freed from their neighboring muscular attachments leaving the spinal ligaments and vertebral column separate. The findings in these dissections may be summarized as follows:

The supraspinous ligaments are rather firm fibrous cord-like ligaments extending between the apices of the adjacent lumbar spines connecting them together. The ligament is not more than 2 mm. in thickness as a rule.

The interspinous ligaments are thick quadrilateral-shaped pearl colored, white membranes attached along the whole length of the inferior border of each spinous processes, from its root to its summit and extending downward to the same parts of the superior border of the spinous process below. The ligament is in reality composed of two folds or layers of fibers, one on either side, with a clearly defined line of separation between them, not noticeable, it is true, when they are covered posteriorly by the supraspinous ligament, but rendered very obvious if the latter are dissected away and a sharp object, as, for example, a needle, is introduced between. It is apparent that if the needle be kept to the median line the interspinous ligaments hold it tightly between their layers and tends in this way to guide it forward, usually without it piercing through either lateral fold. Guided thus it attains with ease and precision the interarcuol space.

As to the resistance of the ligaments it may be said that while the supraspinous ligaments offer some resistance at the start, it is trifling and is easily overcome, and also that the interspinous ligaments offer no obstruction to a good strong steel needle.

Therefore, we feel justified in concluding that instead of the interspinous ligaments being a contraindication to the use of the median route they are, in most cases, a great aid in holding the needle safely to the median plane and directing it thus to the interarcuol space, often, indeed, with unerring precision.

Therefore, it is evident that the objections to median puncture because of the ligaments which must be transversed are not corroborated by studies upon the cadaver in this small series of dissections. Likewise, in the living, we have only rarely encountered a patient in whom the operation by this route could not be successfully performed, despite the fact that many of our own cases were adults and were strong, muscular individuals. We do not doubt, however, that in some patients, especially the aged, these ligaments will be altered to such an extent that they will offer great resistance; but there is every reason to suppose that in such cases the ligamentum subflava will likewise be changed. In fact, it seems plausible to think that ossification of the yellow ligament would be more

apt to occur earlier in life than that of the interspinous ligament owing to the greater range of movability of the spinous processes as compared to the lamina.

The possibility of the needle being broken in the instance of a violently delirious patient is probably slightly greater with the median route than with the lateral, but on the other hand such patients should always be controlled by chloroform anesthesia. In the usual case on the contrary, the lateral route is more apt to be accompanied by this type of accident for the needle more commonly encounters bony obstacles and repeated poorly directed thrusts with the instrument are very common, especially in the hands of an inexperienced operator.

Therefore, since the arguments against median puncture do not stand the test of proof, let us look into its advantages over the lateral route. The median is a clearly defined procedure; it is very simple and is quickly and easily learned by the novice. There can be no doubt that dry taps are encountered less frequently than with the lateral method. This is readily understood, because in lateral puncture the needle must be started at just a certain point and given a definite inclination inward and upward in order to penetrate the subarachnoid space in the median line. The chances of error in the direction given to the needle, either that it may be directed too much inward, causing it to pass entirely beyond the interarcuol space, or too much upward, causing it to impinge upon the vertebral arch above, resulting in both cases in a dry tap, are evidently great. The disadvantages of the lateral route are therefore evident for one who is not experienced in rachientesis.

The liability of injury to the nerve filaments of the cauda equina or to the spinal bloodvessels is less with the median route; in fact, Krönig goes so far as to state that it is only after lateral puncture that cases of nervous affliction due to injury of nerve fibers are observed. In spinal anesthesia it is essential that the dura be penetrated about in the midline so as to assure equable distribution of the anesthetic fluid injected. The same rule applies, also, to a less extent, to the injections of serums. In median puncture the dura is entered exactly in the median line, providing the needle has been directed straight forward, while in lateral puncture one has to calculate the proper direction to be imparted to the needle in order to strike the dura at the particular place desired. In the lateral route the instrument must traverse a deep layer of subcutaneous tissues and a thick mass of lumbosacral muscles, before reaching the ligamentum subflava and the dural membrane. The chances of the needle being plugged and the probability of encountering bloodvessels is greater. Moreover, one must remember that the yellow ligament is thicker and stronger in the lumbar region than elsewhere. Holwell, although an advocate of the lateral route, admits that the resistance which the ligamentum subflavum offers may be so great

that the operator may think he has encountered bone. Although some writers, especially Grey,<sup>24</sup> claim that pain from striking the periosteum of the spine is more intense and common in median puncture, we have never found this to be the case; on the contrary, everything points to the lateral route as being the most painful, since the needle more commonly strikes bone.

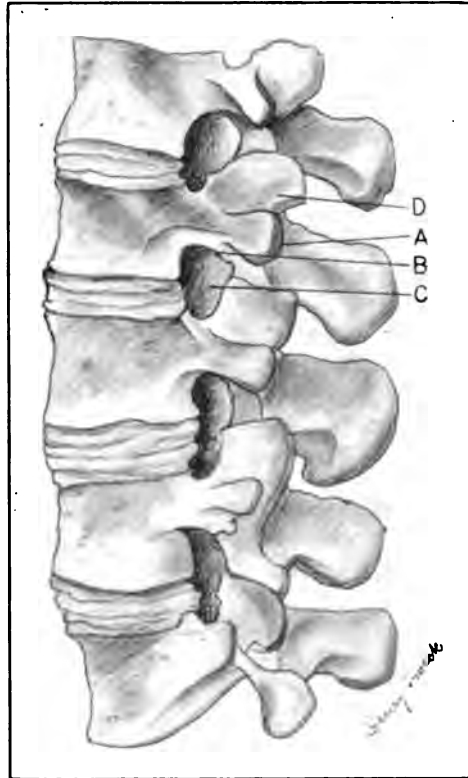


FIG. 1.—Drawn from a prepared specimen in the anatomical department of the Bellevue Medical College, to illustrate the appearance of the lumbar vertebrae of an adult in the normal upright position. The downward inclination of the spinous processes are very evident; this inclination being accentuated by the tubercles on the inferior border. The various processes are indicated diagrammatically by letters: *A* represents the transverse processes, *B* the laminae, *C* the small interlamellar opening through which the needle must pass to reach the subarachnoid space in the lateral puncture, *D* the articulating processes.

A glance at Fig. 1, picturing the lumbar vertebrae in lateral view, will be enlightening in showing the difficulties which the lateral route presents. The inner angle of the narrow space between the laminae represents well the interlamellar opening through which the needle must enter (Fig. 6). This opening is of a sufficient size, if one had some guide by which to reach it, to act, for example, like the inter-

spinous ligaments in median puncture; but there is no such anatomical help or path to be followed in lateral puncture; instead, the needle is plunged to a depth of 2 to 2½ inches into a mass of subcutaneous and muscular tissues, hoping that chance and the estimated inward and upward direction of the needle will guide it to the interlamellar opening. It is evident that the probability of striking

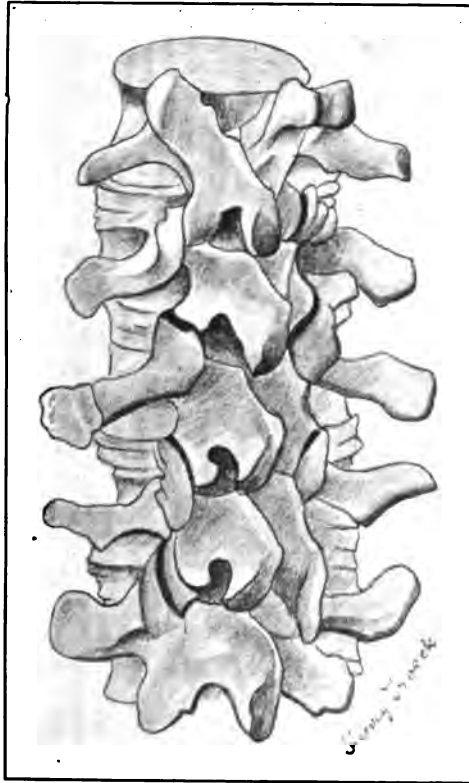


FIG. 2.—The same, posterior view. The inclination of the vertebral spines are very definite and also the sharp character of the superior border and the downward and outward direction of the external surface of the spinous process and laminae. The entirely different structure of the inferior border of the spinous process will be noted, also its notched and rounded contour just where it opens into the vertebral canal.

bone is great and that repeated thrusts may be needed before the space is reached, thus often rendering uncontrollable a patient who at first was docile and quiet, further adding to the difficulty of the operation. The difference between the two routes may then be summarized by saying that in the lateral, chance plays a great part, while in the median the operator arrives usually with unerring precision at the interarcuol space.

THE DIRECTION OF THE INSERTION OF THE NEEDLE IN CHILDREN. Quincke,<sup>1</sup> in his original and classic description of the technic of lumbar punctures, describes the characteristic oval or rhombic shape of the interspinous spaces in children and the horizontal direction of the spinous processes, as noted in a series of studies on the skeletons of twelve children. Upon this anatomical basis Quincke claims that



FIG. 3.—Gives an idea of the appearance of the lumbar region of the spine in an infant, aged four months. The body has been placed downward and with a slight support under the abdomen to bring out the structure of the spine more clearly by causing a certain amount of spinal flexion. The lumbosacral muscles have been removed partially so as to expose the various spinous processes and ligaments. Among the points to be noted are the rudimentary character of all the processes, their semi-cartilaginous structure, the amply wide interspinous intervals and the width of the laminae and narrow interlamellar space.

in lumbar puncture by the median route on young patients the needle should be introduced directly forward perpendicular to the spines. Among the very few authors who follow closely the precepts of the master upon this point are Delmas<sup>22</sup> and Sophian. Most authorities, however, advocate that a slight upward inclination be given to the needle. Thus Gray,<sup>24</sup> Fisher,<sup>25</sup> Spear,<sup>12</sup> Ruhräh and Mayer,<sup>6</sup> Kap-

lan,<sup>17</sup> Testos<sup>26</sup> and Devraigne<sup>27</sup> are all of this frame of mind, the latter author basing his opinion upon experimental work on infant cadavers.

Clinically, we have been impressed by the simplicity of the median route when the needle is introduced in a direction absolutely perpendicular to the spine and with back well arched, so as to increase



FIG. 4.—Illustrating the character of the lumbar vertebrae in a child, aged six years; posterior view. The spinous processes, the laminae and transverse processes are more developed and the process of ossification is more advanced than in Fig. 3. The degree of flexion of the back is very slight and for this reason the separation between the adjacent spinous processes is not nearly so much as that attained in the living subject when the back is well arched in preparation for rachientesis. Yet even here the interspinous interval is definite and free from any bony obstruction.

the width of the interspinous spaces. The needle then encounters no bony obstruction and is passed into the subarachnoid space without difficulty. At the postmortem table we have been able to examine the structure of the lumbar region of the spine in a number of children. The spinous processes are broad, quadrilateral-shaped projections, running in a perpendicular direction to the body of the vertebrae, with a straight even superior and inferior border having

practically no inclination upward and without any downward projecting tubercles upon their summit. The typical appearance is

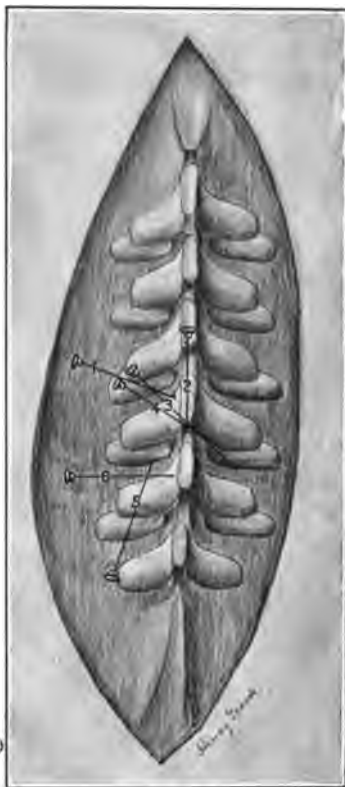


FIG. 5.—Illustrating the appearance of the five lumbar and first sacral vertebrae in a child, aged eight years; posterior view. The development of the various processes is more advanced than in Fig. 4. To show the simplicity of the median and the difficulties of the lateral route, owing to the diverse directions the needle may take, a number of needles have been introduced into the spine in various positions. All have been introduced as in left lateral puncture except No. 2. In 1 the needle introduced at an improper level has impinged upon the spine of the fourth lumbar vertebrae of the same side. In 2 the proper method of introducing the needle by the median route in the fourth lumbar interspinous space is shown. In 3 the instrument has been inclined too much inward and not sufficiently forward, and as a result it has passed through the interspinous ligament and is buried in the soft parts of the opposite side. In 4 it has pursued a similar course but encountered the transverse process of the opposite side. In 5 it has been directed too much upward and not enough toward the midline, causing it to strike the transverse process of the same side. In 6 the needle introduced at an incorrect level has impinged on the spine of the fifth lumbar vertebrae. The chances of error in lateral puncture are therefore obvious. In a very similar manner, but much more easily, owing to the distance to be traversed, the needle may go astray in the case of an adult spine.

shown in Figs. 3, 4, 5 and 6. When the back is flexed practically no alteration is produced in the direction of the lumbar spines but the height and depth of the interspinous spaces is increased considerably,



the processes becoming widely separated. This separation is made possible by reason of the thickness of the intervertebral fibrocartilagenous disks in the lumbar region, permitting a close approximation of the anterior portions of the vertebral bodies.

By reason of the structure of the lumbar spines in childhood it is evident that the only proper method of introducing the needle is in

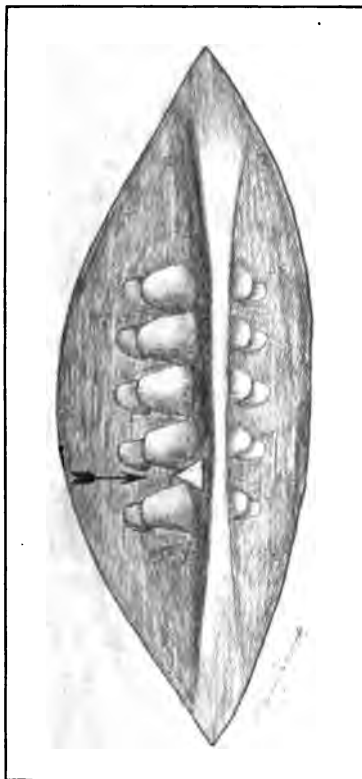


FIG. 6.—Illustrates the appearance of the lumbar region of the spine in a young child, the spinal ligaments remaining intact. The arrow indicates the small triangular area in the interspinous ligament and the ligamentum subflave through which the needle must pass in lateral puncture in order to reach the interarcuol space. The area is proportionately smaller in an adult, and the depth to which the needle must be introduced is of course much greater (6 to 9 cm.) further adding to the difficulties of reaching the desired point, the more so as there is no definite guide to follow.

an exactly perpendicular direction, following in this way the direction of the spinous processes themselves. Any upward inclination imparted is unnecessary and increases proportionately the dangers of a "dry tap."

This method of inserting the needle is applicable to children below the age of puberty. It is about this time that the character of the lumbar spines begin to change, assuming more of the adult type,

necessitating, often, certain modifications in the technic which will be explained below.

**THE DIRECTION OF THE INSERTION OF THE NEEDLE IN ADULTS.** The consensus of opinion among authors using the lateral route in adults is that the needle should be introduced inward and slightly upward. The degree of this angular inclination, however, is not specified. Thus, Holwell,<sup>11</sup> Foote,<sup>4</sup> Ruhräh and Mayer,<sup>6</sup> De Ridder,<sup>8</sup> Ker,<sup>14</sup> Kaplan<sup>17</sup> and Holmes<sup>5</sup> consider that an upward and inward direction should be imparted to the instrument. Musser<sup>28</sup> alone mentions the angle of inclination to be used; he believes that the needle should be held at an angle of 45 degrees with the surface of the body. Elsberg<sup>29</sup> also draws attention to the fact that occasionally the needle must be introduced obliquely upward to avoid the bone. In punctures by the median route, Ker<sup>14</sup> states that the needle should be inserted either absolutely straight or with a slight upward slant. Barker,<sup>21</sup> using the same route, contends that a slight upward inclination be given. Quincke<sup>1</sup> in his classic article upon the subject advocated in lateral puncture that the needle should be held rather upward than otherwise, at the same time drawing attention to the character of the intervertebral spaces in the adult. They are not oval or rhombic-shaped openings, as in the child, but, on the contrary, are covered more or less by the inclination downward of the vertebral spines. In a later presentation<sup>30</sup> he remarks that "the spinous processes run generally horizontal, still sometimes are inclined downward or possess on their points hook formed downward bended extensions."

In Gray's text-book on *Descriptive Anatomy* the lumbar spinous processes are described as thick, broad, somewhat quadrilateral projections, horizontal in direction, thicker below than above and termination by a rough uneven border.

We have studied the character of the lumbar vertebræ in a small number of adult skeletons, and in three dissections upon adult cadavers previously referred to. Our findings have been somewhat similar to those of Quincke, and may be summarized as follows:

The lumbar spines are not always as horizontal and straight as one is apt to believe for text-book descriptions. In a high proportion of cases in the normal upright position the lumbar spinous processes have a distinct downward inclination which is considerably increased by a projection of the tubercles on the inferior border. This is evident from Fig. 1, showing the lumbar vertebræ from behind and from lateral view. When the spine is well flexed the interspinous intervals are widened, but the direction of the vertebral spines are only slightly altered. They become less overlapping, however, and this renders possible the introduction of a needle between in a perpendicular direction at an angle of 90 degrees, which in the normal position of the spine would have been impossible, owing to the fact that it would have been impinged upon the

superior border of the spinous process of the vertebræ below. In some instances, however, even with the back well arched, it is impossible to introduce the needle in a straight perpendicular direction, without striking the superior border of the spinous process below. Under such conditions the operator, thinking that he is unable to enter by the median line, usually directs his needle more laterally, and as a result it impinges upon the outer surface of the lamina. A mistake in direction has then been made which can only be rectified by the complete withdrawal of the needle and its reinsertion. When a bony obstacle of this character (superior border of the spinous process below) is met the operator should withdraw the needle just sufficiently to allow its being directed upward at an angle of 60 to 45 degrees.

Just in what proportion of adults it is necessary to introduce the instrument at an angle of 60 to 45 degrees, by virtue of the construction of the lumbar spines, is difficult to state; it is certainly in the minority the number could be approximated 10 to 15 per cent. As a general rule it may be said then that if the back can be well flexed the needle should always be introduced directly perpendicular to the spine at an angle of 90 degrees. This direction will succeed except in a minor percentage of cases. If bone is encountered the instrument is then directed obliquely upward at an angle of 60 to 45 degrees, and this will always be followed by the disappearance of the bony obstruction and the entrance of the needle into the subarachnoid space except in rare instances.

When there is slight opisthotonus and the back cannot be well flexed or the lower limbs well drawn up, owing to rigidity, the spinous processes cannot be separated, and a perpendicular puncture at an angle of 90 degrees is commonly unsuccessful. Under such circumstances it is advisable to insert the needle in an upward direction, usually at an angle of 60 to 45 degrees. In a position of marked opisthotous many operators consider puncture is impossible without an anesthetic. Our experience does not confirm this viewpoint, and it seems to us that by the median route, with a sufficient inclination of the needle upward (45 degrees or less), the interarcuol space can be attained.

In the aged especially the spinal ligaments are not so pliable and the intervertebral disks are less compressible; hence, spinal flexion is more difficult to obtain, and for this reason it is usually advisable in such patients to give the instrument a decided direction upward.

There is an anatomical arrangement which we have encountered in our dissections and which no doubt also helps to explain some of the cases in which no fluid is obtained by a perpendicular introduction of the needle, but which yields fluid if the needle is directed upward. The superior borders of the lamina are rather sharp with their prominent external surface slanting and inclined downward and outward. The inferior borders, on the contrary, are notched

and rounded, presenting the opening of the vertebral canal. Naturally a needle directed at an angle of 90 degrees and in the median line, and deviating slightly from its course, may easily impinge upon the superior border of the lamina, and will then be directed outward away from the vertebral canal. On the contrary a needle directed upward at an angle of 60 to 45 degrees and veering from its median course would either pass immediately into the vertebral canal or else, impinging on the rounded inferior border, would thereby be directed inward, reaching the desired point.

RESUMÉ. There is considerable confliction of opinion among authors upon many of the details of the operation of rachientesis. The route for puncture and the direction of the needle are among the points over which there is much controversy. Yet it is unquestionable that these two parts of the operation must be properly carried out in order to bring it to a successful termination. From clinical experience, which was later confirmed by experimental work upon the cadavers of adults and children, both in the dissecting room and at the autopsy table, we believe the following conclusions upon these points are warranted:

1. The median route is greatly superior to the lateral route for the puncture of children by reason of its simplicity. The lumbar spinous processes of children are rudimentary, rather short, horizontally directed and partly cartilaginous processes, which have a fairly even superior and inferior border, somewhat rounded at the summit of the process but without any tendency to overlap. When the spine is well flexed there exists between them an interval (the interspinous space) which is usually quite wide and which permits the introduction of the needle in the median line without any liability of touching the spines. The distance to be traversed is very small, especially in young children; in fact, after the needle has pierced the skin and the supraspinous ligaments it quickly glides through the interspinous ligaments and is immediately felt to penetrate the dural sac. In the case of young children and infants a slight resistance is offered by the rather tough supraspinous ligaments, but this is easily overcome and is the only difficulty encountered in the median line. The quickness, simplicity and certainty of the result and the easy facility with which a beginner acquires the method are among the many points in favor of the median route for young patients.

2. The construction of a child's spine differs from that of an adult's. At an early age the vertebræ are not distinct and separate bones connected by ligamentous attachments as they are later in life; but, on the contrary, they appear *en masse*, partly cartilaginous and united into one piece, from which the individual bones are separated only with difficulty. The line of cleavage and the degree of movability is more definite between the spinous processes than elsewhere. The laminae are rather short, wide, and the interlamellar

spaces are directed rather obliquely downward and are quite narrow, further adding to the difficulty of the lateral route.

3. Many authors base their objection to median puncture in the adult on the thickness and resistance which they claim the interspinous ligaments offer, especially in muscular individuals. To determine the basis for this argument the author studied these ligaments on several adult cadavers. This study gave the following findings: The supraspinous ligaments are rather tough, fibrous, cord-like ligaments extending between the summits of the adjacent spinous processes. The interspinous ligaments are rather thick, quadrilateral-shaped, pearl-colored ligaments attached along the whole length of the inferior border of each spinous process from its root to its summit and extending downward to the same parts of the superior border of the spinous process below. The ligament is in reality composed of two folds and layers of lateral fibers, with a clearly defined line of cleavage between. For this reason when a needle is introduced in the median line after penetrating the supraspinous ligament it enters the interspinous ligament and passes along between its two layers, and is thus guided forward with precision to the interarcuol space. Marked resistance is not encountered even in muscular individuals except in rare instances. Therefore, instead of the interspinous ligament being a contraindication to the use of the median route they are in most cases a great aid in holding the needle safely to the median line and directing it thus to the interarcual space, often, indeed, with unerring precision.

4. Among the advantages of the median line for puncture of adults are the following: It is a clearly defined procedure and is quickly and easily learned by the inexperienced; no calculation is necessary as to the direction inward and upward to be imparted to the needle in order to reach the interarcual space as in lateral puncture. The liability of striking bone and bending or breaking the needle or wounding the periosteum is less. The possibility of passing beyond the limits of the interarcual space is reduced to minimum while it is ever present with the lateral route. The injury of nerve filaments or spinal bloodvessels is less likely to occur. No difficulty is experienced in penetrating the dural sac exactly in the median line, as in the lateral route, which point is important for spinal anesthesia and serum injection. The chances of the needle being plugged by the tissues traversed and of bloodvessels being encountered is less with the median than with the lateral route. Dry taps are less common in median puncture. In other words, chance plays a great part in lateral puncture, while in median the operator arrives usually with unerring precision at the interarcual space.

5. In the case of children the needle should be introduced directly perpendicular to the spine (at an angle of 90 degrees) and in the median line. This method is obviously the rational one to employ, as a study of the characteristics of the lumbar spinous processes

and the shape of the interspinous spaces shows. The needle then encounters no bony obstruction and is passed into the subarachnoid space without difficulty. Any upward inclination increases proportionately the danger of a dry tap.

6. In adults the anatomical structure of the spine differs from that of a child, and this fact influences markedly the manner of insertion of the needle. The lumbar spinous processes are not as horizontal as at an early age, but have a distinct downward inclination, which is considerably increased by a projection of the tubercles on the inferior border. Flexion of the spine widens the interspinous intervals but does not appreciably alter the direction of the spines themselves. With the spines well flexed, however, the interval between the adjacent processes is widened sufficiently to allow the introduction of a needle in the majority of instances in a perpendicular direction (90 degrees) to reach the subarachnoid space without encountering bone. In some cases (a decidedly minor percentage) it is impossible to introduce the needle in a perpendicular direction without having it impinge on the bony obstruction of the superior border of the spinous processes of the vertebræ below. In such instances the needle's course should then be changed by withdrawing it slightly and directing it obliquely upward at an angle of 60 to 45 degrees, and this will always, except in rare cases, be followed by the disappearance of the bony obstruction and the entrance of the needle into the subarachnoid space.

7. It is possible to obtain fluid by the median route in adults even in cases of marked opisthotonos if a sufficiently marked inclination upward is given to the needle.

8. Flexion of the spine is attained only with difficulty in elderly individuals, hence the needle should be introduced slightly upward from 70 to 45 degrees.

9. Certain anatomical configuration of the spine helps to explain why some cases of failure to obtain fluid by the median route, with a perpendicular insertion (90 degrees), may be due to a deviation of the instrument from the median line and its impinging on the superior border of the lamina, while a more upward inclination would have been entirely successful even though a similar deviation of the needle occurred.

The writer wishes to take this opportunity to thank Dr. Abraham Sophian for first demonstrating to him the simplicity of rachientesis by the median route, thus affording the incentive to the present study.

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## PHYSIOLOGICAL CONSIDERATIONS IN THE IMMEDIATE TREATMENT OF DANGEROUS HEMATEMESIS.\*

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I. THE CONDITION OF THE CIRCULATION. In hemorrhage the fall in arterial pressure from great loss of blood volume is counteracted, as far as possible, by certain reactions in the body, the chief of which is the contraction of the peripheral arterioles, the result of stimulation of the vasoconstrictor center. This contraction is a gradually increasing one as the hemorrhage progresses (Wiggers), except that at a late stage there is paralysis of the vasoconstrictor center with general vasodilation (Pilcher and Sollmann). As the cerebral and the cardiac coronary arteries are not under the control of the vasoconstrictor center the general peripheral constriction does not include them, and consequently there is a greater flow of blood

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through these unconstricted arteries, a provision in nature to maintain the efficiency of the vital organs, the brain and the heart. Indeed, the coronaries at least not only do not contract but may even dilate, for it has been shown by Wiggers that after hemorrhage the coronary flow equals or exceeds the normal flow even though the systemic arterial pressure is below normal.

The heart therefore does not suffer so much as other organs, and as shown by cardiographic tracings, maintains its normal contractile power even after considerable loss of blood. (Wiggers.) There is therefore ordinarily no reason for giving strophanthin or digitalis or any other drug to maintain the heart, and there is contra-indication to any drug, such as nitroglycerin, to overcome the general peripheral constriction, which is not only a necessity for the maintenance of the blood supply to the heart and the vital centers of the brain, but may be, in addition, the means of shutting off the bleeding vessel itself.

II. THE LIMIT TO HEMORRHAGE. Of much greater importance than the total amount of blood lost is the rate of loss, a sudden loss being a more serious matter than a gradual depletion to the same degree. But even with rapidity much blood must flow before the patient is in real danger. Experimental work indicates that it requires a rapid loss of from 4.5 to 5.5 per cent. of the body weight of a normal dog to cause death (Levin), and if we apply the minimum of these figures to man it would mean that the fatal point is not reached in a man of 150 pounds until he has rapidly lost  $6\frac{3}{4}$  pounds of blood or about  $6\frac{1}{2}$  pints. That this is correct for the human being has been shown by Gjestland, for in statistics bearing on the power of the human to lose blood and yet recover, he reports the cases of two women with postpartum hemorrhage who each lost about 3000 grams ( $6\frac{3}{4}$  pounds) of blood and recovered, one woman being discharged from the hospital on the fifteenth day and the other on the twenty-seventh. If an illness antedates the hemorrhage, as in the case of cancer, chronic ulcer or cirrhosis of the liver, the fatal amount will, of course, be less, according to the extent and character of such preceding illness. But if the hemorrhage recur at several hours' interval the total fatal amount will be more, for the blood volume tends to be restored by absorption of tissue fluid, and the blood-making organs rapidly furnish a supply of blood cells.

III. THE CESSATION OF BLEEDING. The natural process by which hemorrhage is checked is the obliteration of the opening in the bleeding vessel. In some cases this is favored by the retraction of the vessel, but in all cases it requires the formation and retention of a clot at the opening. The clot, however, because of the force of the blood flow, does not form at once at the opening in the vessel, but beginning at some distance away reaches back by accretion until it covers the opening; then it stops the bleeding. The distance at which the clot thus begins to form is determined by the force of the blood ejection and the degree to which the blood is held in contact



with the injured tissues; therefore as the stomach is a hollow viscus it may permit a great deal of blood to spurt out into its lumen before any of the blood succeeds in clotting and clinging to the tissues in the immediate neighborhood of the lesion. This is one reason for the frequency of large hemorrhages from the stomach. Hence, in the treatment it is desirable to ensure *contraction of the stomach*, a state which not only tends to permit the bleeding vessel to retract instead of remaining on the stretch, as in a distended organ, but also, because of the larger and more closely packed folds of mucous membrane, may result in a retarded flow of blood.

In these cases of bleeding there is, as a rule, no thrombosis in the lumen of the vessel until some time after the opening of the vessel has been sealed. Hence the surface clot may at first be easily loosened, and if loosened permits resumption of the bleeding. Other factors which may interfere with the formation of the clot or may cause a clot to break loose are:

1. Active peristalsis.
2. Undue temporary increase of blood-pressure, such as may result from the accelerated respiration and increased heart-rate.
3. Sudden accesses of blood-pressure, such as may be brought about by vomiting and by large and rapid intravenous administrations of fluid.
4. Mechanical interference, as by injudicious lavage.

To favor and maintain effective clot formation we need therefore a *quiet contracted stomach, quiet heart and quiet respiration, avoidance of vomiting, and careful watching during the introduction of fluids to restore the blood volume*. The acceleration of the heart and respiration are due not only to direct depression of the vagus center and direct stimulation of the respiratory center, but also to the reflex effects of general nervousness and anxiety. The best remedy for these is a hypodermic of *morphin* which through its effects upon the respiratory and vagus centers slows the respiration and the heart, and by its action on the cerebrum lessens anxiety and nervousness. It also depresses or abolishes peristalsis, and by central action lessens the tendency to vomiting. These are very great advantages. But morphin has the striking disadvantage that while it abolishes peristalsis it also abolishes tone in the stomach wall, so that in large doses it produces an atonic dilatation, a state just the opposite of that desired. To counteract this I would accompany the morphin with a maximum dose of *strychnin*, for strychnin acts to promote tone in the stomach muscles and thus opposes the morphin disadvantage without appreciably counteracting the desired effects of morphin on the respiratory center, the vagus and the cerebrum. Contrary to a prevalent belief strychnin does not activate the circulation. *Atropin* has been employed to counteract the effects of morphin on the stomach, and it does this to some degree; but in the large doses necessary it also annuls the desirable control of the vagus over the heart.

*Lavage.* If the stomach remains distended and if there is evidence that the bleeding still continues, *i. e.*, that an efficient clot has not formed, lavage, in my opinion, may properly be employed. If the bleeding seems to have stopped or if the patient gags severely on the introduction of the tube, lavage should not be employed. Lavage should, of course, be carefully done, the amount of added fluid being rather small. That there is an advantage in the use of excessively hot or excessively cold water is rather doubtful, for such liquids are prone to set up peristalsis. The use of the tube has an added advantage in that it permits the introduction of a coagulant after the stomach is washed out, an ideal time for it to come in contact with the bleeding tissues.

*Emetin* has been employed to stop the hemorrhage, but its pharmacological action shows that there is no justification for its use for such a purpose. It is a depressant of the vasoconstrictor center (Sollmann), and at once or following a transient vasoconstriction it produces definite vasodilatation (Pellini and Wallace). Furthermore, Howell states that it retards clotting by causing a deficiency in the fibrinogen of the blood.

IV. VENOUS HEMORRHAGE. As the venous system of the stomach empties normally into the portal vein, and the average mean portal blood-pressure is only 10 mm. of mercury (Starling), a venous hemorrhage from erosion due to a stomach lesion is without great force and usually quickly ceases. Therefore, except in the rare cases of perforation of a very large vein, such as the portal, splenic or superior mesenteric, venous hemorrhage from an ulcer or cancer is probably never great. However, in the cases with portal congestion, as in portal thrombosis or cirrhosis of the liver, the portal venous pressure is much higher than this, and consequently venous bleeding is more vigorous and more prolonged. But even then the bleeding ceases as soon as the portal congestion disappears, and in all but exceptional cases is prone to be beneficial to the patient rather than harmful.

But in just these cases of portal congestion a serious venous hemorrhage with which we may have to deal is that from the submucous veins of the lower third of the esophagus. At one end these connect with the coronary veins of the stomach and at the other end with the systemic venous system, so that they form a free communication between the portal and systemic veins. In portal obstruction they undergo a compensatory dilatation (Quain), with a marked tendency to become prominent in the esophageal wall and to form varices. (See Figure.) Thus they are subject to traumatism or to spontaneous rupture, and when ruptured are a source of hemorrhage from both the portal and the systemic venous systems. Furthermore, owing to the comparative smoothness of the esophageal mucous membrane, the blood finds no hindrance to its flow and little tissue to clot upon and cling to. Moreover, as shown by Whipple and Hurwitz, in cases of hepatic cirrhosis there is a marked diminution in the fibrinogen content of the blood and consequent

retardation and imperfection in the clotting; or, as stated by Clowes and Busch "even in the presence of an adequate proportion of thrombin, the clot formed is not sufficiently tough to effect the desired result." Hence these hemorrhages, though venous, may be large and are occasionally fatal. As the blood is brought up by vomiting they are not usually distinguished with certainty from gastric hemorrhages; and as the passage of a stomach tube would be dangerous it should be the rule that *in hematemesis if there is evidence of portal congestion, lavage is absolutely contra-indicated.*



Roentgen-ray picture of the esophagus in a case of portal thrombosis, death being due to hematemesis. Autopsy by Dr. John H. Larkin at the City Hospital, New York. The veins were injected with a red-lead mixture.

**V. MEASURES TO RETARD THE EJECTION OF THE BLOOD.** For this purpose the substances in use are the local vasoconstrictors, such as epinephrin, and materials of colloid nature to increase viscosity.

*Epinephrin* (adrenalin) acts locally to constrict the bleeding vessel and so to retard the flow of blood and permit clotting. It is administered by mouth in amounts of 4 to 15 c.c. (1 dram to 1 ounce) of the 1 in 1000 solution of the hydrochloride, diluted with about 2 to

5 times as much water to make bulk enough to coat the stomach. It has the disadvantage that it tends to induce strong peristalsis. The same may be said of pituitary. Though when administered intravenously epinephrin distinctly increases the coagulability of the blood (Cannon and Gray) by increasing the prothrombin (Grabfield), and may constrict the bleeding vessel itself, it cannot safely be used intravenously because of its marked effect in heightening the systemic blood-pressure.

*The colloid materials* in use are gelatin and acacia, which on injection intravenously or perhaps subcutaneously tend to increase the blood's viscosity and so to act mechanically to retard the escaping blood. We shall speak of these later.

VI. MEASURES TO INCREASE THE BLOOD COAGULABILITY. Besides the actions spoken of above there is a natural progressive increase of the blood's coagulability as hemorrhage continues (Drinker and Drinker, Gray and Lunt). Indeed, so strikingly does hemorrhage tend to cease at the point of syncope that Crile has advised a return to the method of the older physicians who would sit the patient up and perform venesection to hasten the onset of syncope. J. Kaufmann reports seeing Kussmaul successfully carry out this principle in a case of extreme hemoptysis.

If by the natural processes adequate clotting fails to occur we may attempt to supply an agent that will hasten the formation of the clot. Accepting Howell's terminology for the sake of uniformity the clotting elements in the plasma of the circulating blood are: prothrombin, calcium and fibrinogen and in addition some thrombin; the anticlotting elements are antiprothrombin and antithrombin. In clotting the prothrombin is liberated, and, taking up calcium, changes to thrombin; and this free thrombin quickly precipitates the fibrinogen in the form of fibrin, *i. e.*, it produces clotting. In the intact vessels clotting is prevented by the anticlotting elements, which hold the prothrombin and thrombin in neutral combination. Normally there is a great excess of anticoagulants in the blood, so that much prothrombin and even thrombin may be added to the circulating blood without thrombosis resulting. (Davis.) In hemorrhage the disintegrating blood platelets and leukocytes and the tissue juices of the injured tissues supply the lipid thromboplastin (cephalin, cytozyme, thrombokinas); and this has such an affinity for the anticoagulants that it breaks up the prothrombin combination and sets free the prothrombin to take up the calcium and coagulate the fibrinogen and so form the clot.

In profuse hematemesis there is no reason to suspect a deficiency in any of the coagulation elements of the blood, but owing to the rapid passage of the blood beyond the injured tissues, as in a hollow viscus like the stomach or esophagus, there are cases in which the prothrombin is not liberated quickly enough to form a clot at a point sufficiently close to the bleeding vessel to bring about cessation of the bleeding. The clotting takes place at the normal rate,

yet not quickly enough to be of use where it is wanted. Therefore, we think of the possibility of employing agents to favor clotting, even though, on testing, the coagulation time of the blood proves to be normal. For this purpose there are several substances for use both locally and systematically. They may be called *coagulants*, and the principal ones in use are:

1. Cephalin or thromboplastin.
2. Extracts of the blood-platelets.
3. Blood serum, the serum derivatives euglobulin and coagulose and defibrinated blood.
4. Whole blood.

The increase of coagulability through the local application of one of these coagulants can readily be comprehended, though it requires that the remedy be kept in contact with the bleeding tissue for several minutes. But the cessation of bleeding after the intravenous or even subcutaneous injection of a small amount of a coagulant is less well understood. Doubtless the administered element, if it acts at all, does so by changing the relations between the clotting and anticlotting elements present in the blood, and it may do this either by supplying a coagulative element, such as prothrombin, by supplying substances to neutralize the anticoagulant elements or by exerting some activating effect upon the blood-forming tissues. The coagulants can hardly be of use to check an immediate profuse hemorrhage, but they may be of value in a continuous small hemorrhage or in preventing a recurrence of profuse hemorrhage. The dose of any coagulant needs to be repeated frequently, as its action is short-lived.

*Cephalin*, or *thromboplastin*, acts by taking up the antiprothrombin and antithrombin and setting free the needed prothrombin and thrombin. It is marketed under the titles *Thromboplastin-Hess* and *Kephalin*. They both contain the physiological lipid cephalin or thromboplastin, and both are prepared from brain tissue, though by different processes. *Thromboplastin-Hess* is a solution in Ringer's solution of tissue juice from the brain with a fine suspension of brain tissue. It is preserved by 0.3 per cent. of trikresol and may be sterilized by boiling. Hess verbally recommended to me a dose by mouth of 4 c.c. (℥j) in 15 c.c. (℥ss) of water every half-hour for three or four doses, but the manufacturers recommend 20 c.c. (℥v) diluted twelve to fifteen times with water. Dilution does not affect its coagulating power. It has been given in amounts up to 60 c.c. (℥ij) in a day without any toxic effects. It is also used subcutaneously or intramuscularly in amounts of 10 c.c. (℥iiss) at a time. The subcutaneous dose is painful. *Kephalin* is an ether-acetone-alcohol extract of brain evaporated until the yellow fatty or lipid residue remains. It is not destroyed by boiling. For use by mouth or intramuscular injection its dose is 10 to 30 drops in physiological saline repeated every six or twelve hours. It corresponds in action with *thromboplastin-Hess*. It seems to be rapidly absorbed from

the alimentary tract, for Howell found that a solution given by mouth showed a lessening of the coagulation time in as short a period as forty minutes.

Kephalin and thromboplastin have also been introduced intravenously, but as they supply the material to produce coagulation of the blood, and so have a tendency to bring about thrombosis in the vessels, the procedure is a dangerous one. In 1 per cent. solution Mannheimer and Wang employed thromboplastin-Hess intravenously in tuberculous hemoptysis in twenty-two instances and noted no apparent benefit from any dose. In its undiluted form Wang injected 5 c.c. into the ear vein of a rabbit, and the animal died almost immediately, with a firm clot in the veins of the neck and in the right auricle, extending to the ventricle. Hess gave intravenously 2 c.c. (3ss) of a 10 per cent. solution to a rabbit and shortened the coagulation time by one-half, though there was no clotting in the body. In dogs Howell found that an intravascular injection of kephalin, 0.1 gram per kilo, shortened the coagulation time from one-third to one-half without any intravascular clotting, the effect lasting for at least one or two hours. Apparently, therefore, a weak solution intravenously is of no use and a strong solution is not without danger, at least for any but hemophiliacs, who have an excess of anticoagulants in the blood. It is a question then whether any amount that would be effective could be used without danger. I have the word of Dr. Hess that the substance should never be used intravenously.

*Coagulen* is a powder prepared from blood-platelets by fractioned centrifuging, followed by desiccation and dilution with lactose. It is claimed that it is a preparation of lipoid material and that 1 gram (gr. xv) of the powder represents 20 grams (3v) of dried blood. It is readily soluble in water and may be sterilized by boiling. According to Howell the platelets of blood yield both prothrombin and thromboplastin and the action of coagulen is that of thromboplastin. In gastric hemorrhage the local action may be obtained by the administration of 20 to 60 c.c. (3v to xv) of a 10 per cent. solution by mouth. Fonio, its introducer, recommends 50 to 75 c.c. (1½ to 2½ oz.) of a 3.5 per cent. solution intravenously and a similar amount subcutaneously, stating that the subcutaneous injection of a stronger solution is painful. From the intravenous use there is the same danger as in the case of thromboplastin.

*Blood Serum.* This is a plasma from which have been removed not only the blood cells but also the coagulative elements of the clot. It has therefore lost part of its power to induce clotting. It contains prothrombin and thrombin in combination with antithrombin, but it lacks fibrinogen. The prothrombin is intimately associated with its euglobulin fraction. Serum is not a powerful coagulant and does not cause intravascular clotting even when amounts of 200 c.c. or more are introduced intravenously. Yet in some cases it seems to have a value out of proportion to its coagulative power even when

employed subcutaneously, so that it has been considered by some an activating agent, stimulating the production of clot-forming elements. It has the great disadvantage that it contains 6 to 7 per cent. of proteins, and thus unless of human origin exposes the patient to anaphylaxis. It also rapidly deteriorates so that after fifteen days it has lost seriously in potency; therefore fresh serums, as from the human being, rabbit, sheep and horse, are preferable to stock serums. Ox and dog serums are too toxic to human beings to admit of their employment. According to Clowes and Busch human serum is in nowise superior in clotting power to that of the animals mentioned, yet it is preferred because, being homologous, it may be used in much larger quantities with safety. Lee and Vincent state that rabbits' serum is the most potent readily available serum. Rettger thought that the loss of ability of serum to produce coagulation was due to a slowly formed, loose combination of the thrombin with the other constituents, and stated that serum that had lost its potency could be reactivated by the addition of weak alkalis or acids, with subsequent neutralization. Howell has confirmed this finding.

The dose of the animal serums intravenously is 100 c.c. and subcutaneously 10 to 50 c.c. every six to twelve hours. But of fresh human serum I have heard Dr. Willy Meyer say that he has repeatedly injected subcutaneously 400 or 500 c.c., and Judd has reported the use of 180 c.c. of the mother's serum in the case of a baby. It takes two to twelve hours to obtain the separated serum from fresh blood, and, according to Hess, twelve to twenty-four hours for the subcutaneous dose of a serum to influence clotting.

For want of available serum diphtheria antitoxin has been employed and in the past has been found useful, but the refined and concentrated antitoxin at present used contains a very high percentage of protein, about 16 per cent., and this almost entirely pseudoglobulins which have almost no value as coagulants. (Hess.)

*Euglobulin.* On account of the high protein in serum and its rapid deterioration as a coagulant, Hess separated the proteins and found euglobulin to be the important coagulative element. As euglobulin is only about one-third of the total protein a solution of it of the same strength as in the serum represents almost the total coagulative power of the serum with only one-third the percentage of protein. It thus gives a lessened chance of severe anaphylaxis. Hess passes it through a Berkefeld filter for sterilization and adds 0.3 per cent. of trikresol as a preservative. But it does not long retain its potency, and is not at present marketed.

*Coagulose* is a precipitate obtained by treating horse serum with a mixture of acetone and ether. It has the coagulative properties of horse serum and retains its potency for a long time. It is prepared aseptically and is kept dry in sealed glass bulbs containing 0.65 gram (gr. x) of the powder. It is made ready for use by the addition of 8 c.c. of sterile water, the temperature of which is not above

40° C. This amount, representing 10 c.c. of serum, may be employed subcutaneously, intramuscularly or intravenously. To make a satisfactory solution it should be dissolved by rotation of the bulb without shaking.

Blood serum and these derivatives lose their coagulative power when heated to a temperature of 60° to 70° C., therefore cannot be sterilized by heat.

*Defibrinated Blood.* The defibrination removes fibrinogen and blood-platelets, but Ottenberg and Libman state that in the process of defibrinating the blood cells are mechanically injured to some degree, so that their products are present in the defibrinated blood and if the introduced amount is large may cause intravenous clotting.

*Whole Blood.* The treatment of internal hemorrhage by the intramuscular or subcutaneous injection of whole blood in small amounts has recently been recommended (Curtis, Emsheimer, Howard), even amounts as small as 10 c.c. being employed. It would seem to us to have no value above that of serum, except that it may be used at once, while it practically forms a hematoma in the tissue with the usual slow absorption of the clotted blood.

*Calcium* as a coagulant is futile in these cases, for to affect the coagulability of the blood it must be given in huge doses for many days.\*

*Styptics.* The local use of the chemical styptics, such as tannic acid, ferric chloride, Monsel's solution and alum, should be condemned, as they are irritant and tend to cause excessive peristalsis, nausea and vomiting.

VII. MEASURES TO RESTORE THE BLOOD VOLUME. In case the hemorrhage does not cease the volume of the blood is soon reduced so low that the mechanical functions of the circulation cannot be carried on. It is then necessary to add fluid to the circulating blood.

*Transfusion.* We have more faith in the transfusion of blood than in any other single measure, or in all the other measures put together, for it tends to fill the vessels with a liquid of the same physiological nature as that which has been lost, it prevents the lowering of viscosity which would otherwise take place whether the result of hemorrhage or of added saline, and it is not readily lost from the vessels by osmosis. For the transfusion I should prefer the syringe-cannula method of Lindemann or of Unger, for the sodium citrate method (Weil, Lewisohn) and the hirudin method (Satterlee and Hooker) involve the introduction of a substance that prevents clotting, and this would seem to be undesirable in a bleeding patient already much depleted of blood. However, in the use of sodium citrate this factor has proved to be a small one, so that if it is the only method available it may be employed. In using the citrate method I should recommend a strength of 0.25 per cent.

\* For discussion see the author's *Materia Medica, Pharmacology and Therapeutics*, 2d edit., 1918.



of sodium citrate, as we have had clotting occur with the 0.20 per cent. strength recommended by Lewisohn. There are many reported instances in which the bleeding ceased quite promptly following or during transfusion. On the other hand there are cases in which bleeding seemed to recur because of the transfusion, and I might repeat the caution that if the bleeding has stopped the blood-pressure should be watched during the transfusion lest the clot be loosened by an access of pressure.

In severe hemorrhage Bernheim's rule is that transfusion should be performed if the systolic pressure drops to 70; and he affirms that the seriousness of the loss is not to be estimated by the percentage of hemoglobin. I would go further and say that if the hemorrhage seems to be continuous, or recurs in large volume, I should transfuse regardless of either the hemoglobin or the blood-pressure, for owing to the prompt action of the vasoconstrictors, the natural elasticity of the larger arteries, and the acceleration of the heart's rate which follows hemorrhage, the blood-pressure may be fairly well maintained for a time though the total volume of blood in the arteries is considerably less than normal. (Wiggers.) Likewise the hemoglobin drops only as the blood is diluted with tissue fluid. In any case of profuse hemorrhage measures should at once be taken to provide for transfusion, and in spite of Ottenberg and Libmann's warning against transfusion in acute first hemorrhages, I should say with Bernheim, "When in doubt transfuse."

*Other Liquids.* If there is no possibility of transfusion, salt solution, preferably of Ringer's or Locke's formula, may be introduced by rectum, by hypodermoclysis or intravenously. In its intravenous use it should be introduced slowly and its quantity limited to 1000 or 1200 c.c. Physiological salines do not interfere with the coagulation of blood (Crile) and may slightly stimulate the vasoconstrictor center (Pilcher and Sollmann), and where they are given to replace lost blood may maintain the blood volume for a sufficiently long period to save the life of the patient. But they have the disadvantage of increasing the volume but not the necessary blood elements, of decreasing the viscosity of the blood, and of changing its osmotic tension so that some of the fluid is before long lost to the tissues or excreted by the kidneys. But following hemorrhage this loss of fluid from the blood after saline is not nearly so rapid as when the blood volume has not been previously reduced. (Crile.) If the blood-pressure is very low, pituitary liquid or adrenalin solution, 15 minims (1 c.c.), may be added to the saline infusion fluid, the infusion being given very slowly.

Levin made a comparative study of the ability of saline solutions and transfused blood to replace blood lost by hemorrhage. In a number of dogs he let out enough blood to kill, allowing the heart to come to a standstill. When he replaced the lost blood at once with fresh blood by transfusion the heart began to beat again, and

in almost all cases the animal revived and in a very short time had returned practically to normal. When he replaced the blood with saline the heart began to beat again and kept it up for a time, but the animal did not revive. Of course in such a case there was proportionately an enormous amount of saline introduced.

*To increase viscosity* and thus prolong the value of added liquid other than blood, less rapidly diffusible colloid liquids, such as a solution of acacia, 5 per cent. in Locke's saline, as recommended by Hurwitz, or a 1 to 2.5 per cent. solution of gelatin in saline may be employed intravenously. Bogart, Underhill and Mendel found that after the introduction of colloidal gelatin solutions the blood retained the increased volume for an abnormal length of time. Gelatin is prone to contain putrefactive products and is less safe than acacia. Gelatin may also be used subcutaneously, and Lindberg has in this way introduced as much as 400 c.c. of a 10 per cent. solution daily.

To increase viscosity, Schreiber recommends 200 c.c. of 5 per cent. solution of glucose, though he has employed it up to 20 per cent. in strength. Kausch has used up to 2000 c.c. of 5 to 7 per cent. solution of glucose. Kuhn holds that glucose decreases coagulability.

VIII. OTHER MECHANICAL MEASURES. In case of extreme exsanguination it is wise to bandage the limbs, to raise the foot of the bed high, to keep the body warm and perhaps even to bind the abdomen tightly and put weights upon it after the method of Meltzer. For it is necessary to maintain the cerebral and coronary circulations at all costs or the patient will quickly die.

The use of an ice-bag over the stomach is customary and may favor contraction of the stomach. But the belief that the application of cold to the abdomen results in constriction of the splanchnic arterioles is disproved by the work of Tice and Larsen.

IX. SURGERY. It is the consensus of opinion that while surgery may be called for in recurrent hemorrhages, immediate surgery is contra-indicated in the presence of a profuse hemorrhage. It has been estimated by Moynihan that not over 3 per cent. of profusely bleeding gastric or duodenal ulcers could be treated successfully by laparotomy. As a matter of fact, either spontaneously or because of or in spite of the medical measures employed, nearly all hemorrhages cease and are not fatal. So that by the time we have decided that the hemorrhage is not going to cease the patient is beyond the point of safety for an operation. Lindberg, of Faber's clinic in Copenhagen, tabulated 68 cases so severe as to raise the question of an emergency operation. It was decided in all the cases to give medical treatment. Only 5 of them died, and the autopsies showed that not one of the 5 could have been helped by surgery. These statistics, together with statistics from other clinics where operations were performed, convinced Lindberg that surgical measures are

never indicated in cases of acute hemorrhage from the stomach or adjacent bowel. Lund recently said: "I have learned that it is poor practice, when the patient is depleted by hemorrhage, to open the stomach and try to grasp the artery in the bottom of an ulcer."

**SUMMARY.** *The Aims in the Treatment of Profuse Hematemesis* are three, viz.: 1. To stop the bleeding. 2. To overcome its effects. 3. To prevent its recurrence.

*The Treatment is:*

1. Have patient very quiet, lying down, with head low, with a light ice-bag over the stomach and with plenty of fresh air.
2. Avoid unnecessary manipulation.
3. Give a hypodermic of morphin sulphate, 0.015 gram (gr.  $\frac{1}{40}$ ) with strychnin sulphate 0.002 to 0.003 gram (gr.  $\frac{1}{80}$  to  $\frac{1}{40}$ ).
4. Immediately after vomiting give by mouth a solution of thromboplastin, kephalin, coagulen or epinephrin.
5. In a case not of the portal congestion type, if the stomach remains distended and the bleeding seems to persist, lavage with tepid water, and follow this by passing in a solution of epinephrin, thromboplastin, kephalin or coagulen through the tube. In portal congestion cases avoid lavage.
6. Prepare early for transfusion, and as soon as there are indications for it transfuse with careful watchfulness.
7. If there is severe exsanguination, bandage legs and arms, raise the foot of the bed, bandage and put weights on the abdomen, keep up body warmth, and furnish fluid intravenously, subcutaneously and by rectum.
8. If transfusion cannot be done give intravenously Locke's or Ringer's solution containing 5 per cent. of acacia.
9. Finally, have a surgeon at hand to share the responsibility, but do not operate.

*To prevent recurrence* inject subcutaneously every six to twelve hours for one or two days, 10 to 50 c.c. of human, rabbit or horse serum, or a solution of coagulose or euglobulin, or a single dose of 100 to 500 c.c. of human serum; or inject intramuscularly a solution of coagulen, thromboplastin or kephalin.

*If recurrence happens*, resort to surgery, if necessary, preceding the operation by transfusion, (a) after the bleeding has stopped, or (b) if the bleeding continues but has become persistently small in amount.

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## THE DIAGNOSIS OF MITRAL STENOSIS.

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OF all valvular lesions, stenosis of the mitral valve is the most protean in its manifestations. It is most versatile in the way it exhibits itself, sometimes so cleverly disguised that one scarcely suspects the wolf behind the apparent, at other times so outspoken and brazen that a veritable beginner might recognize its true nature at once. Experience with the Cardiovascular Board has reëmphasized a former conviction that of all lesions of the heart valves,

mitral stenosis is the most difficult to diagnose, and hence the most instructive.

A text-book case, or what medical teachers characterize as a "third-year condition," meaning thereby one that is so manifest that even a tyro in medicine can recognize it, offers no difficulty, as the combination of a presystolic thrill, presystolic murmur, snappy first sound at the apex and accentuation of the second pulmonic sound, blaze so clearly the path to the correct diagnosis that none but those who will not see can lose his way. Unfortunately this type of case is not found so frequently in apparently healthy young men who present themselves for military service, as does the aberrant and unclassical variety, which, at hasty examination, often presents no murmur or thrill and whose detection is a matter of some difficulty even after prolonged study. It is the latter type of case that has been found rather frequently by the Cardiovascular Board at Camp Jackson. That we should meet with this subtle variety and not the classical one is not surprising, as the local boards are fully able to recognize the typical and the definite, and these individuals are quickly found to be unfit and are not distributed to the various camps, whereas the unusual cases may be passed undiagnosed.

In the diagnosis of typical cases of mitral stenosis, stress must be laid on the fact that failure to hear a murmur in the upright position should not prevent one from recognizing the valve defect if the quality of the first sound is studied. Particular emphasis has been laid on this point at Camp Jackson, and many cases have been rejected that ordinarily would have entered the service, with the great probability of being discharged later for physical disability. We have stressed particularly the quality of the first sound which oftentimes furnishes the clue to the diagnosis.

1. **QUALITY OF THE FIRST SOUND.** The first sound at the apex in a case of uncomplicated mitral stenosis is in the vast majority of instances so manifestly not the first sound heard in health that one's attention is immediately arrested. It is a first sound that is heard in no other condition so characteristically, and when it is heard it deserves careful study. It has a clear ringing note (not in the sense that it is musically vibrant), a snappy sound that defies description, but may be imitated by grasping the slack of a handkerchief in both hands and pulling it taut, or by tapping forcibly with a staccato blow of the finger the back of the hand, the palm being held tightly against the ear.

Palpation will recognize the forcefulness of the systole and the apex-beat will strike the hand sharply and immediately recede. This systolic shock at the apex is an important feature, particularly in those rather rare instances in which no thrill can be felt. It may be questioned whether similar phenomena are not encountered in other conditions, but there can be no question that when these phenomena

are perceived then the case should be thoroughly studied before one presumes to pronounce him as normal.

Misinterpretation of the foregoing is feared, with the impression resulting that all cases of mitral stenosis exhibit the loud snapping first sound and the systolic shock at the apex. This is not intended, as in the cases in which there is insufficiency as well as stenosis, the striking characteristics of the first sound are masked or lost and a murmur takes its place. Here again one's attention should be arrested long enough to examine the case at length.

2. PRESYSTOLIC THRILL. This is held to be the most characteristic feature of mitral stenosis, but that it is not always present, and when present the case is not always one of mitral stenosis, there can be little doubt. A presystolic thrill that terminates in the sharp quick, receding shock of the first sound generally means mitral stenosis.

Recently Morris and Friedlander<sup>1</sup> have invited attention to a functional presystolic thrill unassociated with mitral stenosis. This type of thrill is felt best in the erect posture and is followed by reduplication of the first sound and a systolic shock. A presystolic thrill is sometimes found in cases of aortic insufficiency, but in this disease one misses the loud snapping first sound of a typical stenosis.

When the thrill is not appreciable in the upright position, as it frequently is not, it may be palpated with the subject in the dorsal, lateral or ventral decubitus. The latter is particularly useful, and several times the thrill has become definite when the patient lay on his abdomen, his head resting on his arms. The thrill is distinctly a thrill, with rapidly repeated vibrations similar to the thrill felt over the neck of a purring cat. The coarse fibrillating movement of the chest wall present in those individuals with thin chest walls, which is visible as well as palpable, must be differentiated.

The timing of the thrill is not always easy, but if one will observe the suprasternal or supraclavicular pulsations and remember that in most of the cases the systolic shock is distinctly palpable, little confusion need arise unless there is marked tachycardia. In the latter instance the thrill itself is difficult to detect.

3. PRESYSTOLIC MURMUR. The murmur of mitral stenosis is the most fugitive and elusive of any murmur of organic origin. It is variable from day to day, from hour to hour, and in one case of our series it changed its character within five minutes. It may be present one day and it may be impossible of detection the next. The more recent the damage to the valve the more varying is the murmur; the older the condition the more constant it is. The time of the murmur is diastolic, and arbitrarily dividing diastole into three parts the murmur may be early diastolic, middiastolic or late diastolic, or may

<sup>1</sup> Jour. Am. Med. Assn., 1918, lxxi, p. 375.

occupy the whole of the diastolic period. Another axiom may be expressed as follows: The more recent the valve defect the later the murmur; the older the condition the earlier. This has reference to diastole and may be expressed as the nearer the murmur is to systole, or the nearer it is to a true presystole period, and the shorter it is in duration, the more recent the lesion; while the farther toward the beginning of diastole it is heard the longer the valves have been damaged.

The quality of the murmur is harsh, as is that of all stenotic lesions. When the murmur is definitely late in diastole (presystolic in time) it becomes more loud as it terminates in the loud snapping first sound (the characteristic crescendo presystolic murmur); or the murmur may be at the beginning of diastole, when it is diminuendo and of longer duration than the true presystolic murmur; or it may occupy the entire diastolic period, starting loud, becoming softer in mid-diastole and becoming more intense as systole is neared. To use a musical phraseology the murmur has a mid-diastolic diminuendo and a presystolic crescendo. These fine variations cannot be detected in a rapidly beating heart but can be well made out in typical cases, with normal pulse-rate.

This murmur should be sought for whenever the first sound has the snapping character mentioned above and may generally be heard if the following recommendations are observed: Not only in the upright position should one listen, but the subject should be examined when he lies on his back, side or abdomen, and in this last-named decubitus a flat bell of a stethoscope (phonendoscope) is very useful. All our suspected mitral stenosis cases we examine in the ventral position, which serves to bring out the murmur very clearly, especially when in other positions its detection was obscure. Exercise often brings out the murmur and auscultation following exertion should always be practised. Remembering the fickleness of the presystolic murmur and the relative constancy of the systolic shock or snappy first sound at the apex it behooves one to become early familiar with the characteristics of the typical first sound of mitral stenosis, so that when such a sound is heard his attention may be concentrated on the task of proving the diagnosis. It is not going too far to insist on the diagnosis of mitral stenosis in the absence of a murmur providing one has recognized the snappy first sound and not mistaken it for the booming of an hypertrophied heart, although no case in our series was diagnosed on this feature alone.

4. ACCENTUATION OF THE PULMONIC SECOND SOUND. In many of the cases of well-compensated mitral stenosis (no auricular fibrillation) the second sound at the third left intercostal space is accentuated and much louder than the aortic second sound unless the second sound is replaced by a Graham-Steell murmur. If there is any doubt about the interpretation of an apical first sound it is as

well to remember that if the sound is that of an hypertrophy of the left ventricle the second aortic will be accentuated, while if it is the typical snappy first sound of a mitral stenosis, the pulmonic will usually be louder than normal.

5. BLOOD-PRESSURE. There is really only one valvular defect which is associated with fairly definite blood-pressure phenomena—namely, aortic insufficiency. Blood-pressure of itself is of no help in the diagnosis of mitral stenosis, but it has been interesting to note how frequently the pressure was above normal in stenosis and how rarely in insufficiency (well compensated).

6. HISTORY is ordinarily of great importance, although in our series rheumatic fever was by no means constant. In the army reliable histories are hard to obtain. Hemoptysis is a frequent symptom and should always excite suspicion.

Realizing the care that is required in many cases of mitral stenosis before a correct diagnosis can be made the Cardiovascular Board at Camp Jackson was instructed that with the draft increments special study of all abnormalities of the quality of the first mitral sound should be made, and all such cases, including cases exhibiting a diastolic murmur, no matter where it was found, were to be referred to me for detailed examinations. Those of us who have seen draft examinations can readily appreciate how difficult it is to devote much time to the study of the abnormal; it suffices to recognize the case as unfit for military service and to diagnose it, but further than this it is rarely possible to go. For this reason the cases noted above were withdrawn from the line and were brought to my office, where they would be away from the excitement of the examinations and where protracted study could be carried out in quiet surroundings. It was due to the skill and hearty coöperation of Lieutenants Harris, Byrnes, Feinglos, and Captain Hastings, of the special board, and of Captains Langhorst, Metzger, McDonald and Lieutenant Anderson, of the Depot Brigade, that the material for this paper was collected. In all 36 cases of mitral stenosis were diagnosed from a draft increment of about 15,000, 24 being "pure" cases and 12 associated with insufficiency.

Of etiological factors in the 24 cases of pure stenosis, rheumatic fever, chorea, tonsillitis and growing pains are the most important, although the history of growing pains we have found difficult to obtain, as few individuals have heard of this phrase. In some instances, rheumatic fever, chorea and tonsillitis appear together in an individual's history, and hence the total number of diseases given below exceeds the total number of cases, a discrepancy which is easily understood.

Rheumatism occurred 12 times, tonsillitis 10, growing pains 9, chorea 6; in one instance symptoms, chronologically speaking, were referred to an attack of pneumonia and diphtheria; in 12 individuals there was no history of previous infection (*sic*).



On physical examination following the outline of the Government form for cardiovascular examinations, cyanosis was observed 14 times, pallor 4 times and in 6 cases the appearance was negative as far as these two phenomena were concerned. However, we feel that the individual with stenosis has a somewhat characteristic appearance. He is rarely a large man, generally poorly developed, undernourished in aspect, and his face is drawn, the eyes look sick and there is a dusky, turgid appearance of his face and hands and coldness of the extremities. The board has individually come to recognize a stenotic facies, and men with this appearance were put aside for study even before they were palpated or percussed.

**THRILL.** A presystolic thrill ending in the characteristic systolic shock was felt 22 times. Not always was the thrill felt when the patient was erect, but generally the thrill was more definite when he lay on his back, and always the thrill and the shock could be well felt when the subject lay on his abdomen.

**MURMUR.** In all of the 24 cases a murmur was heard. Sometimes not in the erect posture but usually in the recumbent position, and always best in the ventral decubitus.

**SNAPPY FIRST SOUND.** This was heard typically 19 times; in the 5 cases in which it was not heard a systolic murmur, accidental or without significance, muffled it. The second pulmonic was found to be accentuated over the normal 15 times; in the 9 cases not accentuated a diastolic murmur was heard.

Hypertrophy of the heart was found in but 4 cases. Irregularities were found but once, and this was an extrasystolic arrhythmia. The systolic blood-pressure was sometimes quite high but the average of the 24 cases was 13.2 mm. Hg. The diastolic pressure was 78.

Cabot in 1914<sup>2</sup> published a paper on 200 autopsied cases and 116 not autopsied cases, which as regards numbers makes the 24 cases of our series appear insignificant. However, my series has the advantage of having been carefully examined by at least two men, especially trained in cardiovascular work, apart from my own examination, and has the further advantage that these cases were all ambulatory young adult males, who showed so few signs that they were accepted by local boards for military service. We agree with Cabot that cases of mitral stenosis are frequently undiagnosed, but we cannot agree that the average well-trained physician can diagnose only 50 per cent. If one relies on an examination of a few minutes only, omitting examining the individual in the erect, dorsal and ventral and lateral positions, omitting the examination after an exercise test, he will be fortunate if he can make correct diagnoses in even 50 per cent. of the cases. Cabot's conclusions are based largely on clinical records some twenty-two years old, and this is scarcely fair to the modern practitioner.

<sup>2</sup> Tr. Assn. Am. Phys., 1914, xxix, p. 22.

The diagnosis in some cases is most difficult, but in no case impossible, unless the auricle is fibrillating to such an extent that no diagnosis is possible other than fibrillation. The important features of an ambulant case, such as we are now seeing in the army, are a loud snapping first sound at the mitral area, presystolic thrill terminating in systolic shock, diastolic murmur generally late in diastole accentuation of the second pulmonic sound and absence of hypertrophy of the heart on percussion.

These palpatory and auscultatory findings should be carefully sought for before and after exercise, with the subject in various positions, and especially useful will be found the examination of the patient when lying on his abdomen. In the majority of the cases this serves to intensify the three cardinal features, the snappy first sound, the thrill and the murmur, a trilogy which is sufficient to permit of the diagnosis of mitral stenosis.

## REVIEWS

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**A MANUAL OF OTOTOLOGY.** By GORHAM BACON, A.B., M.D., F.A.C.S., formerly Professor of Otology in the College of Physicians and Surgeons, Columbia University, New York; Aural Surgeon, New York Eye and Ear Infirmary. Assisted by TRUMAN LAURANCE SAUNDERS, Assistant Professor of Laryngology and Otology, College of Physicians and Surgeons, Columbia University, New York. Pp. 583; 204 illustrations. Philadelphia and New York: Lea & Febiger, 1918.

THE author is to be congratulated upon such an excellent manual for students and general practitioners. The descriptions are short, clear, and to the point, and the author does not lose you in tiresome details. The descriptive anatomy is useful. The mastoid operation is suitably described, but might have better illustrations. The labyrinthine portion has much better photographs of the operation, and is interesting. The author has made of the Bárány reactions a condensed resumé, and to one uninitiated into the labyrinthine details his work is helpful. The adenoid and tonsil operation is valuable and timely. The book is up-to-date, and should prove useful to many physicians.

N. P. S.

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**MANUAL OF HISTOLOGY.** By H. E. RADASCH, Assistant Professor of Histology and Embryology, Jefferson Medical College, Philadelphia. Pp. 580; 307 figures. Philadelphia: P. Blakiston Son & Co., 1918.

THIS is an expansion of the author's shorter book on histology, and is arranged under the same chapter headings. Thus the first chapter on technic, which occupied 31 pages in the compend, is here enlarged to 55 pages, and this enlargement is typical of all the subjects treated. Many additional illustrations have been selected from other works and some new ones, chiefly photomicrographs by the author, have been added. All these changes contribute to an increase in thoroughness of presentation, and in its enlarged form the book cannot fail to be more helpful to the seeker after histological information.

W. H. F. A.

DISEASES OF THE NOSE AND THROAT. By WILLIAM LAMB, M.D., M.R.C.P., LOND., Honorary Surgeon, Birmingham Throat Hospital. New York: William Wood & Co., 1918.

THIS book, designed as an elementary work, contains many good points, and some not so valuable. It is small and compact, the subject desired is easily located, nearly all the operations are up-to-date, and the author endeavors to make the subject clear to the novice first, adding an excellent summary for the specialist. There are many good photographs of the cadaver which are suitable for anatomy study, but many more are needed to make the subject clear to a beginner. Especially is this true of the operations.

Most young medical men do better operating when they have photographs to guide them, and this book, unfortunately, has very few illustrations of operations, however minor.

It is strange to hear that the guillotine still has its advocates, while the better method of dissection is so lightly dwelt upon. The ear section gives many useful pointers, especially good is the plan of keeping the external canal aseptic.

N. P. S.

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SOME HEADACHES AND EYE DISORDERS OF NASAL ORIGIN. By GREENFIELD SLUDER, M.D., Clinical Professor and Director of Laryngology and Rhinology, Washington University Medical School, St. Louis, Mo. 115 illustrations. St. Louis: C. V. Mosby Company, 1918.

DR. SLUDER'S book marks a decided advance in medicine. It is a pleasure to find such a work which combines the clinical pathological and surgical findings. It has been my observation that the physician who is a pathologist in addition to being a surgeon is a more discerning observer and a much better trained operator, and Dr. Sluder is this rare combination.

The causes of headaches have long been a wilderness for the medical explorer, and many a skilful diagnostician has been caught in the mazes and failed to find the right path to the source of the disorders. Therefore, any work which offers new aids in throwing light into this difficult field of study is welcome. Fortunately, Dr. Sluder's book is not only a beacon light to the family practitioner, but is of great help to the surgeon, as it gives diagnostic pointers with complete descriptions of the operations, amply illustrated by excellent drawings.

Any competent rhinologist who has done modern surgery knows that Dr. Sluder's claims are well founded and deserving of the recognition they will receive. Moreover, the cures cited are real cures.

The turbinectomy operation is unique and well described, promising a quick and effective means of opening the ethmoid and frontal-cell drainage. The technic for injecting the sphenopalatine ganglion

gives minute details for this difficult procedure and will help many young rhinologists over a rough road.

The author gives many case histories, with sufficient data to explain his methods of reasoning, and these should aid other physicians with doubtful cases to arrive at a correct diagnosis. The text is amply illustrated with cuts near the subject, the descriptions are clear and the operations well described, and other old methods are fortunately omitted. Indeed, the book is a most welcome addition to any rhinologist's library, and will afford an evening of pleasure to any well-informed surgeon.

N. P. S.

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PRINCIPLES AND PRACTICE OF INFANT FEEDING. By JULIUS H. HESS, M.D., Professor and Head of the Department of Pediatrics, University of Illinois College of Medicine. First edition. Pp. 338; 20 illustrations. Philadelphia: F. A. Davis Company, 1918.

ORIGINALLY intended as a hand-book for his students, Professor Hess has presented the *Principles and Practice of Infant Feeding* in a clear and practical manner in this little volume, which will doubtless recommend itself highly to the general practitioner.

Its simplicity of style and its lucidity of meaning reduce the difficulties connected with infant feeding to an irreducible minimum.

Dr. Hess very wisely and rightly lays much stress on the great value and importance of breast milk for the young infant.

In the absence of the mother's milk the employment of a wet-nurse is advocated and the management of the wet-nurse is presented in considerable detail.

In treating the subject of nutritional disturbances the views and classifications of Czerny and Finkelstein are closely followed. An index and a very helpful appendix greatly increase the usefulness of the book.

J. H. S.

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CHEMISTRY OF FOOD AND NUTRITION. By HENRY C. SHERMAN, PH.D., Professor in Columbia University. Second edition, rewritten and enlarged. New York: Macmillan Company, 1918.

It is a satisfaction to be able to welcome unqualifiedly such a publication as the *Chemistry of Nutrition*, by Henry C. Sherman, the second edition of which has just appeared. To students of the general topics of metabolism and nutrition, and particularly to internists who want a survey of these fields, this volume should prove of real value.

In studying a large and intricate subject like the physiology of nutrition, it is useful to approach it from several angles in order that what is obscurely or imperfectly expounded by one author may perhaps be more easily and intelligibly grasped through the writings

of another. The opportunity afforded by this book to establish new contacts in this difficult field should therefore be utilized by all who appreciate a terse and dependable presentation of the scientific evidence at hand. The work is an epitome more of the views of others than of those of the author, and it has the outstanding merit of full presentation without such refinement of detail as to make the text difficult of comprehension.

The author discusses the foodstuffs and the digestive processes in the usual order, and these subjects occupy the first third of the book. The fate of the foodstuffs in metabolism and an excellent consideration of calorimetry and its practical application are next presented. Space is then devoted to mineral metabolism and the general topic of foodstuffs in their relation to the deficiency diseases. In two appendices are provided a classification of proteins, and tables giving the usual data of the composition of foodstuffs at large.

Each chapter is followed by a considerable list of references. The book as a whole is modelled somewhat after Dr. Lusk's classical work on the *Science of Nutrition*, but those desiring an easier approach to or briefer review of this subject will peruse the present work to their advantage. It should also serve as a reference work of no small value to all except specialists in this field. R. P.

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GYNECOLOGY. By WILLIAM P. GRAVES, M.D., Professor of Gynecology at Harvard Medical School. Second edition. Pp. 883; 490 illustrations. Philadelphia and London: W. B. Saunders Company, 1918.

IN his preface to this edition, the author states that the book is designed as both a text-book and a general reference book on gynecology. Its completeness of detail makes it unusually fit for both these purposes. The volume, as a whole, has been enlarged by 115 pages. These additional pages include 100 new illustrations. The subject-matter is divided into three parts:

Part I is devoted to the physiology of the pelvic organs and their relation to the different elements of the general organism, including the various glands of internal secretion. This section gives the results of recent investigations in this still undetermined field. An abstract of Loëb's recent work on the corpus luteum appears in this connection, also the very interesting results of ovarian transplantation. The question of organotherapy also is discussed to some extent in this connection. The author makes one feel the close relationship which really exists between the work of the gynecologist and that classed specifically under neurology and psychiatry. He quotes Havelock Ellis as saying: "These facts of morbid psychology are very significant; they emphasize the fact that even in the healthiest woman, a worm, however harmless and unperceived, gnaws periodically at the roots of life." In this second part, too,

an entirely new section has been added, presenting the relation of gynecology to the Freudian theory of sexuality.

Part II is devoted strictly to gynecological diseases, including inflammations; new growths, both benign and malignant; defects of development, as well as the normal embryology of the urogenital tract; malpositions of the pelvic organs; injuries due to childbirth; also a group of special gynecological diseases and a section on general symptomatology.

Part III gives a very complete description of the surgical aspects of gynecology. This is not confined to the generative organs alone, but includes operations on the abdominal wall for hernia, operations of the kidney and ureter, also operations on the bladder and rectum. In closing there is a brief, but very practical, chapter on the technic of examinations and the essentials of postoperative care.

The illustrations, both the half-tones and microscopic drawings, are excellent in every case, being particularly free from the diagrammatic and unreal qualities which characterize the illustrations seen in many text-books. Those in Part III, illustrating the operative procedures, are done by the author himself, and aid particularly in emphasizing and elucidating his methods of operative technic. Altogether, the book succeeds admirably in meeting the needs for which it is designed. Moreover, it not only satisfies the general needs of the gynecologist, as such, but also presents much valuable information in the field of general abdominal surgery. M. G.

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TRANSACTIONS OF THE AMERICAN UROLOGICAL ASSOCIATION. 1917, Vol. XI. A Collection of the Papers Presented before the Society, April 2, 3 and 4, 1917. Pp. 353, with a number of illustrations and photographs. Brookline, Mass.: Riverdale Press, 1918.

THE *Transactions* represent the investigations of urologists in all sections of the country and present their thought on symptomatology, diagnosis, operative technic, laboratory investigations and new instruments. Thomas in describing how surgical intervention may be needed to cope with chronic prostatitis, after giving case reports, concludes with: "(1) Chronic prostatitis may be and is at times a surgical disease, requiring prostatectomy for its most efficient treatment; (2) chronic prostatitis is not infrequently associated with hyperplastic, polypoid, papillary or nodular formations of the mucosa of the prostatic urethra and vesical orifice, demanding removal by treatment coincident with that directed to the prostate; (3) fulguration or high-frequency spark promises to offer the best method of intra-urethral treatment for this purpose." Young and Frontz in discussing the treatment of the lower genito-urinary tract with radium declare that its use in the treatment of carcinoma of the prostate and seminal vesicles in many cases has resulted not only in

marked symptomatic improvement, but in definite reduction of the size and the consistence of the tumor. Pelonze describes certain bodies, which he calls lymphoid bodies, in the prostatic urethra and declares these to be evidence of tuberculosis. His findings if true are very important. The summary of his case records is: (1) There are many cases of advanced urogenital and pulmonary tuberculosis in which these lesions are not present. They have, therefore, no negative value. (2) They are not peculiar to the male. (3) At least 80 per cent. of these patients were in apparently robust health and had never been suspected of any form of tuberculosis. (4) I am of the opinion that these bodies appear very early, and they apparently persist throughout the entire course of the tuberculosis. They have been found in the mildest as well as the most advanced phases of the disease. (5) Sufficient time has not elapsed to venture an opinion as to prognosis, but it has been abundantly impressed upon me that most of these patients do very well if local treatments to the urethra and prostate are avoided and antituberculosis treatment is instituted. O'Crowley and Martland report 13 cases of new growths of the testis, and following out the teaching of Ewing, declare that for practical purposes there exists only one tumor of the testicle, namely, a teratoma.

B. A. T.

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**THE WASSERMANN TEST.** By CHARLES F. CRAIG, Lieutenant-Colonel, Medical Corps, United States Army. First edition. Pp. 239; 3 colored and 10 half-tone plates. St. Louis: C. V. Mosby Company, 1918.

THIS monograph on the Wassermann test describes in simple and clear language the principles of this important test and the technic of the author, which is a modification of the original Wassermann and Noguchi tests, and which is employed in most of the laboratories connected with the Medical Department of the Army. The numerous and valuable contributions to our knowledge of the Wassermann test which have been made by the author and his colleagues are well known and the results are summarized in this monograph, with numerous references to the more important investigations of others during recent years. The results and interpretation of the Wassermann tests in the various stages of syphilis and the effect of treatment upon the reaction are presented clearly and briefly as based mainly upon the personal experience of the author. The concluding chapter is devoted to the Wassermann test, with cerebrospinal fluid and an interpretation of the results, together with brief descriptions of the technic and practical value of other examinations as the colloidal gold test, cell counts and protein tests. The book will doubtless prove of considerable value to both laboratory worker and clinician and go far toward removing certain prejudices entertained against this valuable test.

J. A. K.



# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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**Clinical Report of Non-specific Protein Therapy in the Treatment of Arthritis.**—SNYDER (*Arch. Int. Med.*, August, 1918). In his series of 110 cases the author used typhoid vaccine prepared by the laboratories of the New York Board of Health, indicating, however, that any protein (bacterial, animal or vegetable) may be used. In acute arthritis about 60 per cent. of cases responded by an abrupt termination after one injection (intravenously). After repeated injections in subacute cases marked improvement followed in about 50 per cent., and moderate improvement in another 25 per cent. While in chronic cases (one to ten years' duration) "moderate improvement in mobility of some joints was noted in almost all cases."

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**Studies in Thyroid Therapy.**—JANNEY (*Arch. Int. Med.*, August, 1918). Subjects of these experiments were patients who were able faithfully to adhere to a prescribed weighed diet and accurate in collection of urine and feces. They were placed in separate rooms in a special metabolic ward under specially trained nurses, were allowed no other treatment (except fresh air, walking and rest), and were under observation from three to thirty-five weeks. Dietaries employed were calculated on the basis of Meek's weight-height formula and all food was sampled and analyzed for nitrogen. The thyroid hormone used was prepared and furnished by E. C. Kendall (Mayo Clinic): *Control experiments* were conducted on two twelve-year-old girls (diagnosis: fully compensated endocarditis) and a woman aged twenty-five years

(diagnosis: mild neurasthenia). The earliest observable effects of minute doses of thyroid was a tendency for the positive nitrogen balance to diminish, with diets containing either normal or decreased amounts of nitrogen. The author regards this action as toxic. Cretin Experiments: Subject, a typical cretin of twenty years of age. On a well-mixed diet (2192 c.) of 50 cal. per kilogram patient was given daily 0.5 gm. of fresh gland. Clinically the improvement was marked. There was a jump in nitrogen balance of 100 per cent. and increase in weight. On a *low protein* high carbohydrate diet (2192 cal.), with the same medication, the patient lost weight and there was only a slight gain in nitrogen balance (over athyroid periods). On a bare maintenance mixed diet (a) without thyroid weight was lost and nitrogen balance approached zero, (b) with thyroid nitrogen balance leaped to 1.32 gm. daily, and there was marked clinical improvement. The author here concludes: "The identical amounts of thyroid which caused nitrogen loss with or without toxicity in normal individuals led to a large gain in nitrogen accompanied with improvement in the clinical condition in the case of the cretin. The therapeutic action of the thyroid is therefore anabolic and constructive, not catabolic and destructive." Three cases of exophthalmic goitre were studied in similar manner. The improvement noted was not ascribable to thyroid medication. In drawing a deduction from the pure metabolism experiments the author concludes for cretins that "a high protein or a high carbohydrate diet is less advantageous than a mixed diet containing rationally balanced amounts of protein, carbohydrate and fat." Cases of exophthalmic goitre the experiments showed "the most favorable diet was one in which protein, fat and carbohydrate are present in usual proportions but in increased amounts." As an explanation of the cause of exophthalmic goitre the author presents the theory of a toxic degeneration of normal thyroid hormone when present in the body in excess, pointing out that "many or all the toxic symptoms of Graves's disease may appear in connection with (1) pathological changes in the thyroid gland; that is exophthalmic goitre; (2) as a result of administration of thyroid material or thyroid hormone in excess to normal myxedematous or thyroidless human beings, or animals." Regarding treatment of exophthalmic goitre the author concludes: "In accordance with previous experience the thyroid treatment of toxic cases is inadvisable." On the other hand, cases showing deficiency symptoms should receive judicious thyroid treatment, using about 0.25 mg. hormone iodine corresponding to 4 grains of thyroid tablets.

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## WAR MEDICINE NOTES

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**Prognosis in Trench Nephritis.**—DYKE (*Lancet*, September 7, 1918) has analyzed the after-history of 50 patients, up to periods of within twelve months from the onset of acute symptoms. The original clinical observations were made at a base hospital in France and the later records were obtained from the home hospitals to which the patient had been transferred. The prognosis with regard to life is very good, as

of the 50 patients but 1 died, and he from scarlet fever. The prognosis with regard to perfect restoration to health is fair, as 29 out of the 49, approximately 60 per cent., made a return to complete health. In the other 40 per cent. the health of the patients was permanently damaged. The prognosis becomes worse with increase in age. In persons under thirty-five years the probabilities are strongly in favor of complete restoration, in persons over thirty-five the likelihood is that permanent damage will remain. Arteriosclerosis is not a common immediate result of the condition. No constant distinctive eye changes were recorded. In every case but one the edema disappeared before the albuminuria. The edema usually disappears during the first week, but its persistence during the second week is common. Its persistence after the second week renders the prognosis increasingly unfavorable. The albuminuria, on the other hand, does not cease usually until toward the end of the first month or during the second month. It may persist during the third month and the case still end favorably, but its continuance after the end of the third month renders the prognosis as regards restoration to complete health unfavorable. The author believes that the condition known as trench nephritis differs little from nephritis met with in civilian practice, except in the greater frequency of its occurrence, and that it is either a primary acute nephritis or an exacerbation of preëxisting disease, induced by continued fatigue and exposure.

W. H. F. A.

**Symptoms of Acute Cerebellar Injuries Due to Gunshot Injuries.**—HOLMES (*Brain*, December, 1917) has been able to examine over forty men, during the present war, who had wounds limited to the cerebellar regions of the brain. These showed injuries of different extent and localization, some of them resembling closely the experimental injuries of the cerebellum on which the classical physiological descriptions of this organ are based. Twenty-one of these patients, in whom the symptoms were pronounced, were under his observation sufficiently long to permit of repeated examination and investigation. As a result of this study he aims to describe those disturbances of function which constitute the symptoms of recent cerebellar lesions as objectively as possible and to attempt to analyze complex symptoms into their simpler components. In the majority of patients who survived the lesions were unilateral, involving chiefly one lateral lobe of the cerebellum, and the author's descriptions are based largely on these cases. One of the most prominent symptoms in the early stages of an acute lesion is the loss or diminution of tone in the muscles of the homolateral limbs and to a less extent in those of the trunk on the same side. During the first week or two, striking features are the flabbiness of these muscles to palpation and the ease with which they can be stretched or compressed, and the affected limb placed in unnatural attitudes, without any discomfort to the patient. This cannot be attributed to loss of sensation, as repeated examinations fail to show such loss. This flabby hypotonic state of the muscles, in extensive unilateral lesions, is always limited to the same side, and is usually more pronounced or at least more easily demonstrated, in the upper than in the lower limb. Associated with this flabby, toneless condition of the limbs the patients complain of weakness in voluntary movements of these muscles. The feebleness is always more pronounced in the arm than in the leg, and when tests are repeated

it is found that the affected limbs tire more quickly than those of the opposite side. There is apparent reluctance on the part of the patient to move the affected arm, and when moved there is almost always a marked slowness of the movement as compared with that of the arm on the uninjured side. This slowness is seen not only in initiating the movement, but also in attaining the exertion of full power and in commencing and effecting relaxation. When, however, corresponding muscles of the two limbs are stimulated simultaneously by a faradic current no slowness in either their contractions or relaxations can be detected, and there is no difference in the latent periods of the contractions of the muscles when these are excited reflexly. The author finds that this asthenia is always more evident in the early stages of the injury and diminishes gradually. This condition of asthenia due to cerebellar wounds is distinguished from that produced by lesions of the cortical motor area or of the corticospinal tracts by its homolaterality, by the uniform and the approximately equal affection of all groups of muscles, by the fact that though all voluntary movements are weak none are limited in range and by the fact that there is no tendency for rigidity or contractures to develop. The most commonly recognized sign of cerebellar disease is the so-called ataxia. This irregularity or disturbance of voluntary movement is quite as marked when the patient's eyes are open as when they are closed. In the early stages all movements of the limbs are affected, but the disturbance is more striking in the upper than in the lower limb, and in complex than in simple movements. One patient's explanation of his difficulty in touching finger to lips was as follows: "I do not seem to have the power to do what I want to with my right hand, though if I take hold of anything with it I can grip it all right. If I want to bring it to my mouth I only hit my eye with it; it is drunk; it will not go straight." The performance of a complicated action by stages, by decomposing the movement into its separate elements, was seen even in patients making their first purposive movements, when still suffering from the early general effect of the wound. This suggests that this decomposition of movement is not always a willed device by which the patient attempts to diminish the inaccuracy of the limbs. Asynergia and dysmetria are striking abnormalities in the affected limbs. Tremor is not such a prominent factor in the early as it is in the later stages of a cerebellar lesion. In many of the serious cases no tremor was noted during the movements of the limbs. Deviations from the line of movement are always seen in recent injuries. Thus one patient found that when he attempted to feed himself with the affected hand it was frequently to his ear that he brought the food, and another that he could not use this hand in smoking as he was afraid of putting the cigarette into his eye. The "rebound phenomenon" was easily demonstrable in all cases with moderate or severe lesions. Thus when the patient's elbows are supported on a table and he is asked to pull each hand in succession toward his mouth against resistance offered by the observer who grasps his wrists; when this resistance is suddenly released the hand of the affected side flies to his mouth or shoulder, often with considerable violence, but the movement of the normal limb is arrested almost immediately. This phenomenon is always more pronounced in the early and acute stages of a cerebellar injury and diminishes gradually as improvement sets in. *Adiadochokinesis*, the inability to execute

alternate movements as quickly and correctly as normal persons, can usually be demonstrated at all joints of the affected limb even when only limited lesions exist, but it is usually more pronounced in the arm than in the leg and in complex than in simple actions. During recovery the slowness, irregularity and awkwardness diminish gradually, but *adiadochokinesis* is one of the most persistent of the ordinary signs of cerebellar injury. Static tremor is, as a rule, seen only in the affected limbs as they become tired. Giddiness is an extremely common symptom after all gunshot injuries of the head, but rarely persists for more than one or two days. This fact throws doubt on the necessary relationship of vertigo to cerebellar lesions. In testing for spontaneous deviation of the limbs with the eyes closed it was found in practically all cases that there was deviation outward by the limb on the injured side. Abnormal attitudes, so striking in Luciani's animals after experimental lesions of the cerebellum, are much less constant and striking in man. As a rule the head tends to be flexed toward the side of the wound and rotated toward the opposite side, so that the chin approaches the contralateral shoulder and the occiput is approximated toward the shoulder of the affected side. It is noticeable, too, in some cases that the limbs did assume unnatural attitudes or would be placed in postures which the patient would tend to avoid in a normal limb. When a patient who is able to leave bed is placed on his feet his whole body sways irregularly and he is usually in considerable danger of falling, especially toward the side of the wound and backward. Nevertheless, he can generally maintain his equilibrium. The patient can stand as well with his eyes closed as when they are open. When with eyes open his attention is diverted, even if only by conversation, he becomes more unsteady and is in greater danger of falling. When he attempts to walk he has even greater difficulty in preserving his equilibrium, though almost all men with unilateral lesions succeeded in walking unaided on the first day they left bed; this varied between eight and seventy-one days after the infliction of the wound. In walking along a straight line he deviates more or less toward the affected side. These difficulties in walking and standing seem to be connected with the disordered condition of the muscles of the affected side. Many have regarded the cerebellum as an organ concerned mainly with the maintenance of equilibrium, but this hypothesis finds no support, according to the author, in the examination of these men. When a man who has recently left bed attempts to progress on his hands and knees he exhibits a very striking similarity, both in attitude and progression, to a dog or monkey after ablation of one-half of the cerebellum. Nystagmus is a very common symptom and of the greatest clinical importance. The eyes while at rest are generally deviated toward the opposite side, usually 10 degrees to 30 degrees to the unaffected side of the middle line. When the patient looks at an object held directly in front of him his eyes tend to deviate to the unaffected side and are brought back to the rest-point by sharp jerks of small or moderate range. On looking toward the injured side the nystagmus is more pronounced, the rate of the oscillations as observed in several patients ranging between twenty-three and thirty years in ten seconds. As time goes on the nystagmus becomes less regular and less characteristic, although it may persist for weeks or even months. As this nystagmus was present even when the wound was small and relatively

superficial it is extremely probable that it is due to damage of the cerebellum alone and not necessarily to involvement of the labyrinth or of Deiters's and Bechterew's nuclei. Speech is affected in most cases in which the lesions are recent and severe; in fact, in a few patients speech was unintelligible for a time. The speech has a "sing-sing" character, slow and drawling, but at the same time tending to have a scanning effect. A striking feature is the apparent effort necessary to utter a series of syllables or a sentence, this being associated with excessive facial grimacing. Often many syllables were uttered explosively. These defects improve rapidly, as a rule, but may persist for even two or three months. Striking alterations in the reflexes are not prominent or very obvious symptoms, although in unilateral lesions the reflexes may sometimes be unequal. The change can be seen best in the knee-jerk. In a few cases during the acute stages of the illness this was absent on the side of the injury but normal on the other side. In other cases the homolateral jerk is at first feebler and less easy to elicit. No differences were detected in the superficial reflexes. No disturbances of sensation were found. Nor was there any disturbance of the nervous mechanism for appreciating and discriminating weights. Though the patient often could not compare correctly weights placed at the same time in his two hands a series of tests on the difference-thresholds for the two hands showed there was no loss or defect in the appreciation of weights on either side. The inability to compare the two weights with the two hands is attributable to the impaired condition of the muscles themselves of the injured side. No case was seen in which the vermis alone of the cerebellum was injured, but cases were studied in which the vermis and one lateral lobe were injured. In these cases the symptoms did not differ in nature from those in lesions of one lateral lobe, though in extent of the damage the functional disturbances are somewhat greater and recovery less rapid when the vermis also is involved. The only special features of vermis injury noted were greater difficulties in speech, more pronounced tremor and greater difficulty in movement of the head and trunk when the patient sat up. No new symptoms were found when both sides of the cerebellum were injured, but the symptoms were bilateral and consequently there was much greater functional derangement of all muscular activities; speech was practically unintelligible and the patients could not sit up or even hold up the head unaided. In regard to the subject of functional localization in the human cerebellum the author believes that the experiences of this war will probably settle the question. Although he finds that his observations lend no support to the theory of focal localization in the cerebellum cortex, he does not believe the problem to be finally solved. W. H. F. A.

**Effect of Exercise upon Undernourished Men.**—JANSEN (*Deutsch. Arch. f. klin. Med.*, December, 1917, cxxiv, 1). *Abstract:* According to the author the official ration of the town of Munich contained in March, 1917, 1600 calories and 9.7 gm. of nitrogen, which is the equivalent of 60.6 gm. of protein. This ration was given to several men who were occupied as interns in the medical clinic of Friedrich von Müller and nitrogen balance experiments were carried out upon them for six to thirty-one days, after the manner of Chittenden. Prior to the experiments the men had been for some time on short rations, especially as

regards the protein element. It is stated, however, that the average loss in weight since the war began was about 5 kg., which certainly does not indicate excessive emaciation. The average weight of the subjects was 62 kg. While partaking of the above diet each man lost weight daily and also very nearly 2 gm. of nitrogen. This loss was attributed to the deficiency of calories in the dietary, for the addition of 500 calories in the form of sugar resulted in maintenance of the body weight as well as in nitrogen equilibrium. *Translation:* All the previous experiments were made upon people who were either inactive or were doing light work only. It remains to consider the behavior of the nitrogen metabolism of people who accomplish heavy work when partaking of an insufficient diet. The subjects, Ebert, Legène and Beholz, abstained from muscular exertion during three days and then they walked together over level ground distances of 18, 20 and 25 km. (11, 12.5, 16 miles) on three successive days. This was accomplished in a driving snow storm, while underfoot there was mud and melting snow, so that tramping was exceptionally difficult and wearisome. The diet remained the same throughout the experiment and contained 60 gm. of protein and 1628 calories, the official Munich ration of the time. The labor of making such a walk was in itself not excessively great and yet the subjects returned home each day overfatigued and exhausted. Each of the subjects, one one occasion, was forced to drive home in a wagon during a part of the return journey, so great was the fatigue experienced. One of them (Ebert) on his return fell into a state of prostration through weakness. The skin was pallid, respiration shallow and quickened, pulse small and slow, temperature subnormal, profuse sweating from the whole body surface; there was no acetone in the urine. Another of the subjects (Legène) gave indications of similar symptoms on the second day. Apathy and psychic depression were present in all three men during the evenings of these days of exertion. The experiments present two different findings as far as the protein metabolism is concerned. In one person the protein metabolism was not increased as the result of the muscular work. In the other two persons the nitrogen deficit increased about 1 gm. daily above the increase which accompanied the low calorie diet. This corresponds to an increase of about 10 per cent. in the total protein metabolism. These results may be thus summarized:

TABLE SHOWING THE RESULTS OF INSUFFICIENT FOOD DURING PERIODS OF REST AND EXERCISE IN MAN.

Subject.	Period.	Calories.	Food. N.	Excreta, N.	Body, N.
Ebert	Rest	1630	9.61	11.83	-2.22
	Work	1628	9.54	12.70	-3.16
	Difference				-0.94
	Rest	1630	9.61	11.55	-1.94
Legène	Work	1628	9.54	10.76	-1.22
	Difference				+0.72
	Rest	1630	9.61	10.81	-1.19
	Work	1628	9.54	11.78	-2.22
Beholz	Difference				-1.03

The average weight of the three men was at this time 57 kg. A complete explanation of this increase in the quantity of protein metabolism is not yet possible. . . . Two of the men (Legène and Ebert) were subjected to respiration experiments twelve hours after the second and third days of walking. These experiments had to be carried out at so late an interval because the persons concerned were too exhausted on their return from their walks to be satisfactory subjects for experimentation. Both experiments yielded surprising results, both as regards the duration of the after-effects of the exercise and the height of the metabolism. . . . In the present series of experiments high respiratory quotients were found twelve hours after the walk was finished. Although the height of the respiratory quotients fell during the progress of the experiment the average of all the determinations was about unity. The explanation of this high value lies in the irritable condition of the subject. The subjects who had formerly yielded themselves freely to this form of experimentation no longer had either the willpower or the physical energy requisite for accomplishing an exact experiment and fell into a state of excitement, which was manifested by the increased respiratory movements. The ventilation of the lungs was abnormally increased. There must have been materials circulating in the blood which acted as stimuli upon the respiratory center. . . . To what extent organic acids are responsible for this phenomenon remains for further experimentation to decide. (*Translator's note:* The average increase in the basal metabolism of Legène after exercise amounted to 50 per cent., or from about 1440 calories to 2160 for twenty-four hours. The smallest measured increase in a single determination amounted to 30 per cent. It is evident that resort to unrationed foodstuffs must have been necessary in Germany at this time for the preservation of the power to do physical work.) G. L.

**Premiere Seance Consagree a la Biologie De Guerre.**—MAJOR W. B. CANNON, United States Army, makes the following the basis for discussion of traumatic shock: 1. Persistent low arterial pressure: This depression is the central and peculiar feature of shock and is a measure of its degree. 2. Concentration of corpuscles in capillaries: The difference between capillary and venous erythrocyte counts in shock may be as much as 2,500,000 corpuscles per centimeter (Bethune observations). 3. Concomitant variations of the degree of shock and body temperature: The blood-pressure falls as the shocked man becomes cold and rises as he is warmed. 4. Reduction of the alkali reserve, *i. e.*, of the sodium bicarbonate of the blood in many cases of shock: The reduction is often so great as to constitute acidosis in Van Slyke's definition (Bethune observation). 5. A correspondence between the degree of reduction of the alkali reserve and the degree of lowering of arterial pressure in shocked men. 6. Damage to the circulatory control: If a low blood-pressure has lasted a long time, nothing will cause a permanent rise of blood-pressure (Dijon experiments clinical observations). 7. A marked sensitiveness of a shocked man to ether or chloroform anesthesia, which induces a dangerous reduction of an already low pressure (Bethune observations and Dijon experiments). 8. A tolerance of nitrous oxide and oxygen as an anesthetic without fall of blood-pressure (Bethune observations and Dijon experi-



ments). The explanation of these facts is as follows: 1. The low blood-pressure is due to cardiac weakness, for if arterial pressure is raised by adrenalin or by cerebral compression the ear works effectively against the high-pressure. It is not due primarily to lack of vasoconstrictor tone, for raising the blood-pressure by aortic compression in a rabbit with a cervical sympathetic cut on one side results in the flushing of the denervated ear, but not of the ear still connected with the medulla (Seelig and Joseph). 2. The low pressure is explicable as a consequence of blood being out of circulation or stagnant on some part of the vascular system (anemia). The anemic blood is not in the abdominal veins as commonly supposed (see testimony of British surgeons, *Lancet*, 1917, ii, p. 727). It is not in the arteries, for in that case arterial pressure would not be low. 3. Concentration of blood in capillaries: The observation suggests that the "lost blood" of shock may be largely stagnant in capillaries, concentrated there by extravasation of lymph. Concentration is seen also in shock produced by injection of histamine (Dale and Laidlow). 4. Variation of shock with body temperature: Cold causes an accumulation and concentration of corpuscles in the capillaries. The blood count is higher in a cold than in a corresponding warm part of the skin. Cold therefore would augment the anemia of shock and warmth would diminish it. 5. Reduction of the alkali reserve: This results from too great lowering of arterial pressure. If the pressure is lowered to 80 mm. of mercury by lessening cardiac inflow through increased intrapericardial pressure there is no reduction of the alkali reserve; if lowered to 70 mm. the reserve begins to decrease; if lowered to 60 mm. it decreases more rapidly (Dijon experiments). Records of human cases made at Bethune confirm these experimental observations. A "critical level" in a falling blood-pressure lies at about 80 mm. of mercury, systolic pressure. As arterial pressure falls the circulation rate is slower and the oxygen supply to the tissues is less. Inadequate supply results in partial oxidation, with development of lactic acid (Araki) and with consequent reduction of the alkali reserve. 6. The lower the arterial pressure the lower the alkali reserve: From the foregoing considerations this result is to be expected. 7. Damage to the control of the circulation: Nerve cells are specially sensitive to oxygen-lack. If blood-pressure continues below the critical level sensitive structures are injured. Vasoconstrictor tone gradually diminishes (Erlanger). Finally, transfusion or infusion causes no permanent rise of pressure; the effect is that seen after the medulla is destroyed (Dijon experiments). 8. Sensitiveness to ether: The injured vasoconstrictor center is further depressed by the anesthetics, ether and chloroform, and blood-pressure consequently drops to a lower level.

*Cause of Shock.*—1. It is not due primarily to loss of vasoconstrictor tone for reasons stated above. 2. It is not due to fat embolism, for: (a) too much fat is required to check the flow of blood through the lungs (2 c.c. per kilo in dogs); (b) venous pressure in man is not raised as in experimental fat embolism; (c) the peculiar hyperpnea or apnea seen in experimental fat embolism does not occur in man. 3. It is not due to "apapnia." The excessive respiration demanded by this theory is not seen in human cases. 4. Evidence that it is due to the effect of tissue injury (experiments in coöperation with Bayliss and at Dijon; Cf. Delbet, Quenu); (a) the crushing of muscles in a hind leg is followed

by a fall of arterial pressure beginning in about twenty minutes and reaching in about an hour a shock level; (b) the effect occurs even though nerves to the leg are severed; it is therefore not of nervous origin; (c) if the bloodvessels (iliac artery and vein) of the leg are tied and the muscle injured the pressure drops only after the blood flow is restored; (d) if a shock pressure has been caused by muscle injury, tying the vessels may be followed by a progressive rise of pressure to the normal level; (e) the effects of muscle injury may pass away with spontaneous recovery of pressure; (f) the lowered pressure after injury is not primarily due to extravasation of blood and lymph into the injured tissues. The measured amount is insufficient.

*Application of the Foregoing.*—Considerations to the treatment of shock. 1. Every effort should be made to check loss of body heat from the shocked man and to restore to normal a lowered body temperature. Avoid exposing the body; use hot drinks, hot-water bottles, blankets and hot air. 2. Raise as soon as possible an arterial pressure, which persists below the critical level, in order to avoid the damage from oxygen want. 3. Use preferably transfusion of blood to raise pressure, for thus, in addition, oxygen carriers are added to the circulation. In the absence of blood use Bayliss's gum-salt solution, which raises pressure (by increasing volume) and thereby causes more rapid circulation and better employment of the corpuscles as oxygen carriers. 4. Use a tourniquet to separate a shattered, useless part from the rest of the body. Apply it as near as possible to the injured region, amputate proximal to the tourniquet and before removing it. If a tourniquet, used to stop bleeding, is to be left in place for a long period apply it at the most distal effective location. The surgeon must be guided in his decision to save or sacrifice the part by questions of viability and gross infection in the excluded region and danger to the rest of the body from its retention. 5. If ether is used in operating on a shocked man, begin to raise his blood-pressure by transfusion of infusion as soon as the anesthetic is started and continue the process during the operation. Use preferably nitrous oxide and oxygen, in a ratio not exceeding 3 to 1, preceded by morphin. Avoid always deep anesthesia and cyanosis. (The Bethune observations were published in reports to the Subcommittee on Shock of the English Medical Research Committee and in the *Jour. Am. Med. Assn.*, February 23, March 2, 1918. The Dijon experiments have not been published in detail.) P. R.

## THERAPEUTICS

UNDER THE CHARGE OF

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**Botulism: A Further Report of Cases Occurring in the Pacific Coast States.**—DICKSON (*Arch. Int. Med.*, 1918, xxii, 483) reports that prior to September, 1917, there were 23 recorded outbreaks of botulism in the United States in which 87 persons were poisoned and 58 died. In

addition to these there were at least 6 instances in which domestic fowl were poisoned and showed symptoms identical with those produced experimentally by feeding with the toxin of *Bacillus botulinus*. Of the 25 instances of poisoning of human beings or domestic fowl in which the source of poisoning was determined, 17 were shown to have been caused by the ingestion of home-canned vegetables or fruit. Since September, 1917, there have been at least ten additional outbreaks of botulism affecting human beings and four affecting domestic animals. Of these fourteen outbreaks, thirteen were due to the eating of home-canned vegetables or fruits, and from six of these the *Bacillus botulinus* was recovered. In six of the outbreaks the victims were poisoned simply by tasting the contaminated material and in several others the poisoning was caused by salad prepared from uncooked home-canned vegetables. It is probable that the various methods employed in the home-canning of vegetables, etc., are efficient in preventing ordinary spoilage, but they are inefficient if the raw material happens to be contaminated with the spores of *Bacillus botulinus*. These outbreaks indicate that it is unsafe to eat or even to taste home-canned products before boiling, the toxin of *Bacillus botulinus* being rapidly destroyed by heat. Dickson points out that it is of the utmost importance that those who are directing the home-canning industry should recognize that the present methods are not entirely safe. Since the toxin of *Bacillus botulinus* is quickly destroyed by heat the authorities should instruct the people that the danger of poisoning from home-canned products can be avoided if all such food is boiled before it is eaten or even tasted.

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#### **Value of Amyl Nitrite Inhalations in the Diagnosis of Mitral Stenosis.**

—MORRISON (*British Med. Jour.*, April 20, 1918, p. 452) emphasizes the importance of excluding from the army all men suffering from mitral stenosis. While the diagnosis of advanced cases is relatively simple the diagnosis of incipient cases is more difficult. These early cases do not complain of subjective symptoms, and reliance must be placed on physical signs. Accentuation of the first sound and accentuation and reduplication of the second are the most reliable of the physical signs of incipient mitral stenosis, but are often present in "irritable heart." The differentiation between these two conditions is essential. A presystolic murmur or thrill, or both, is the positive and crowning sign of mitral stenosis. In the absence of one or the other it is inadvisable to make a diagnosis of this lesion. Among patients very near the borderline there are a number who present no suggestion of mitral stenosis when examined standing but who show unequivocal signs when lying down. There are a number who present inconclusive signs when standing, but signs of stenosis become clear in the recumbent position. A further group exhibit no conclusive signs on standing or lying. In these the diagnosis becomes clear when they lie after exercise. At the Military Heart Hospital all cases are auscultated standing and lying and lying after exercise. Amyl nitrite is used as a further test. Its action, like that of exercise, is to increase the flow of blood through the A-V ring, a change which favors the production of the murmurs in question. Amyl nitrite inhaled from a 3-minim capsule (until a reaction is evident) will often bring to light a clear presystolic or full dias-

toxic murmur in a patient lying on his back who had exhibited no murmur previously. It will therefore render an early mitral stenosis diagnosable. In some instances a presystolic murmur disappears under amyl nitrite. It is suggested that such a murmur is not due to mitral stenosis, but is a Flint murmur associated with aortic regurgitation.

**Clinical Study of the Frequency of Lead, Turpentine and Benzoin Poisoning in Four Hundred Painters.**—Nearly one-half of all the 402 painters examined by HARRIS (*Arch. Int. Med.*, 1918, xxii, 129) gave evidence of active or latent lead poisoning. All the men examined were engaged in indoor work. Harris classifies the cases as follows: Group I 163, or 40 per cent. Active cases of lead poisoning in which the clinical symptoms spoke frankly for saturnism. Lead was demonstrated in the urine of 65 per cent. of these. Group II. 35, or 8.7 per cent. Latent or inactive cases. In these the clinical symptoms were few, but lead was invariably present in the urine. Group III. Borderline cases in which the clinical findings were suggestive. Group IV. Normal cases. Colic was present in over one-half of the active cases. It was complained of in 3 latent, 9 borderline and 8 negative cases. The severity, frequency and duration of the attacks varied greatly. In some cases the colic would last for as long as forty-eight hours. Magnesium sulphate seemed to be the cathartic of choice and in some cases a daily dose was taken as a prophylactic. Headache occurred in 46 per cent. of the active cases; it was usually severe and frontal in type. Only 3 cases of lead paralysis (wrist-drop) were found. Diminution in muscular strength was noted in over one-half of the active cases. No psychoses were found. The "lead line" was found in only 14 per cent. of the active cases. Harris believes that the blue line on the gums, supposed to be so characteristic of plumbism, is of little significance and is rarely found in those who apply reasonable oral hygiene. Lead was demonstrated in the urine in 65 per cent. of the active cases and in all of the 35 latent cases. The author emphasizes the importance of examining the urine for the presence of lead in the diagnosis of lead poisoning. Granular degeneration of the red blood cells was of rather infrequent occurrence, and, like the lead line, is not considered by Harris to be of much diagnostic value. Marked anemia and loss of strength were very common, occurring in 42 per cent. of the cases. Arteriosclerosis was found in 26 per cent. while evidence of nephritis occurred in 8 per cent. of the cases. Heart irregularities associated with myocardial degeneration were found in 11 active cases. Backache was an extremely common symptom though whether this was due to plumbism or to the strain on the muscles resulting from posture, the author was unable to determine. He did not find that lead poisoning interfered with the Wassermann reaction. Bronchitis was a very common complaint. The author believes that this is due in part to the inhalation of turpentine, benzol and other volatile substances used in painting. Of the pregnancies occurring among the wives of these painters, from 20 to 25 per cent. terminated in miscarriages. The home conditions of nearly all of the painters were found, on the whole, to be good. This does not support the theory that saturnism is due to poor social conditions. The use of alcohol did not appear to be a predisposing cause in lead poisoning. The article closes with a series of sane recommendations for the prevention of occupational diseases among painters.

## OBSTETRICS

UNDER THE CHARGE OF

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### **Is the Purgation of Patients just before Operation Justifiable?—**

ALVEREZ (*Surg., Gynec., and Obst.*, June, 1918) states that some purgatives are irritant poisons which must be removed quickly from the body; this interferes with intestinal absorption and upsets the balance of salts, both cause pathological conditions and weaken the body. The dehydration of the body and the disturbance of the balance in salt is known to be bad, especially before an operation, after which there may be hemorrhage and vomiting. When magnesium sulphate is given there may be an increased amount of fluid in the bowel which greatly complicates any operation upon the intestines. In operations upon the colon liquid contents are much harder to control than solid masses. When purgatives act there is an increase of bacteria in liquid feces and increase in absorption of toxins, and more bacteria are absorbed through the mucous membrane. Undigested food may be carried into the colon to supply increased food for bacteria. The even flow of material from the stomach to the anus is disturbed by making some parts of the bowel weaker than normal and thus more irritable. Thus purgatives cause flatulence and disturbance, and when the bowels move frequently during the night, loss of sleep results. This is especially trying for a patient wearing a large cast or with a broken leg or other painful lesion, which causes suffering when the patient moves. Should there be intestinal obstruction a gangrenous appendix or badly diseased Meckel's diverticulum, or adhesions forming around pus, purgation may directly cause death. Purgation causes the bowel to react so poorly to drugs that after operation it may be difficult to meet postoperative emergencies. When the bowel has been emptied by starvation and purgation it is difficult for the colon to resume its normal activity; it must be filled and distended to a certain extent before it will empty itself of its contents. Children and nervous women sometimes begin vomiting during the night before the operation showing that the purgative which has been given causes the beginning of the trouble, and etherization usually causes it to become active. The suggestion is made that food be given as late as possible before operation, that only enemas be used before operation and that these be avoided if not absolutely necessary. That water and solid food be given by mouth as soon after operation as possible and that purgatives be avoided both before and after operation whenever this can be done.

**Puerperal Septic Uteropelvic Thrombophlebitis.**—TURENNE (*Surg., Gynec., Obst.*, June, 1918) reports the case of a multipara suffering from puerperal septic infection, upon whom he operated. In the right broad ligament a thrombosed uterine vein was found and also

thrombosis in the veins of the left broad ligament extending into the spermatic zone, no infiltration of the cellular tissue was observed. Owing to the location of the lesion the right hypogastric vein was ligated and ovarian vein on the left. The first was tied about the level of the promontory and 3 cm. of the posterior median line. The tie was made about 1 cm. beneath the bifurcation. The ligature was made near to the pelvic wall and there was slight bleeding as the stitch passed through the thickness of the broad ligament. In addition to this measure a fixation abscess was produced; the patient had a very painful congestion about the joints coinciding with the development of the fixation abscess. The abscess was incised and the patient began to improve. She finally made a good recovery and the thrombosed veins all disappeared, with the exception of a small-sized vascular cord, which was a remnant of the vein. The writer believes that puerperal septic thrombophlebitis has signs, symptoms and clinical evolutions which should call attention to its development. In more than half the cases there is a tendency to recovery, but the high mortality justifies modern methods of treatment. Surgical intervention by ligature is rational and the transperitoneal route is the preferable one. It is advisable to ligate all efferent venous trunks of the genital zone. It is very rarely necessary to resect or evacuate the thrombi in these veins. The results obtained from direct intervention on the thrombosed veins have been sufficiently encouraging to warrant new attempts at operation to fix definitely the field of operation. When there is permanent bacteremia, when the thrombi are inaccessible and when there is pyemic foci in the viscera, operation on these veins is not indicated.

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**Status Epilepticus in Pregnancy.**—TOMASILLO (*Annali di Obstetricia*, 1917, No. 41, p. 135) writes concerning the resemblance between epilepsy and eclampsia. He describes the case of a patient, aged twenty-five years, five months pregnant, admitted to the hospital under the suspicion that she had eclampsia. On obtaining the history it was found that she had previously had convulsions. The patient had eleven typical convulsions during the first twenty-eight hours after entering the hospital, and these, with the history and negative results in examination of the urine, made the diagnosis of epilepsy probable. The patient was kept in bed and treated by the free use of bromide, with the result that the convulsions ceased and the patient went to term and was delivered normally. As a rule, pregnancy does not increase the severity of epilepsy, but, on the contrary, epileptic women are sometimes better in health during pregnancy. The differential diagnosis is obtained upon a thorough and careful examination of the urine and an accurate history of the patient.

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**Severe Nosebleed Complicating Pregnancy.**—SOLOMONS (*Med. Press*, 1918, No. 105, p. 123) described the case of a young woman, pregnant for the first time, who had had several slight attacks of nosebleed. When seen by the writer the nose was bleeding profusely. The blood-pressure and urine upon examination were normal. Treatment with coagulose, adrenalin and gauze packing was unsuccessful for five days. About two days after the nose was tamponed, labor terminated in the birth by forceps of a dead female child weighing 5½ pounds. The

child was slightly macerated. On the following day the packing was removed from the nose after having been in place about two and a half days. During the first week of the puerperal period the patient had slight fever, but was able to leave the hospital at the end of the third week.

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**Double Uterus with Torsion of One Cornu.**—MAZZINI (*Semana Med.* 1917, No. 24, p. 630) describes the case of a primipara, aged twenty-two years, who was brought to the hospital suffering from labored respirations, pale and with a facial expression indicating some abdominal complication. There was rapid pulse, fever, dry tongue, thirst, vomiting and pyrosis. The abdomen resembled pregnancy at full terms, the fundus being on the left side and well up toward the ribs. The uterus was irregular in contour and the height of the fundus was 33 cm., which did not coincide with the apparent period of the pregnancy. Palpation of the abdomen gave no clear information. On questioning the patient she stated that the abdomen had enlarged suddenly about two hours before entering the hospital. Examination showed a septum commencing at the vulva which gave the appearance of two vaginae. On palpating on the right side there was apparently connection between this and the left uterus. On section the half of the uterus pregnant was practically at term, very dark in color and with a distinct torsion. This was opened, emptied of its contents and removed. Its cervical pedicle was sutured and covered with peritoneum. The patient was convalescent in twenty days; her wound healed by first intention. On opening the uterus, which had been removed, it contained a well-developed fetus. The placenta had been attached normally, but partially separated and there had been hemorrhage.

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**Injuries of Labor.**—SKEEL (*Cleveland Med. Jour.*, 1918, No. 17, p. 83), from his records of obstetric patients examined from two to six weeks after birth, this writer finds that in many instances, although the patient seemed in good condition immediately after labor, she will develop some abnormal state of the genital tract. He divides these injuries into those of the pelvic floor and outlet, the cervix and vault of the vagina and the ligaments supporting the uterus. He calls attention to the necessity of interrupting pregnancy if the patient goes over term, so as to avoid serious injury at birth. Some of the worst lacerations are produced by posterior rotation of the occiput and the delivery of the head in that position. The pelvic wall is split into the ichio rectal fossae, and this injury is not readily discovered unless a speculum and good light are available. When the patient bears down strongly during labor the head impinges against the upper portion of the levator ani muscle before the perineum itself is in danger of laceration. When the pubic arch is narrow the tendency to laceration is still greater. Ether anesthesia should be used to the point of relaxation when the perineum is very tense. When the bladder prolapses it is not uncommon to have the uterus share in this process. The bladder will prolapse through the anterior portion of the triangular ligament if this be torn and the uterus will follow it. In closing the perineum the muscles and fascia should be united separately with buried catgut sutures, using a Graf needle, and then closing the mucous membrane and skin subse-

quently. To avoid undue strain upon the catgut it is well to use additional stitches of silkworm gut. In closing the cervix attention must be called to the necessity of bringing together the upper angles. In order to be successful, such repair should be undertaken in those cases only which are free from active infection or from gonorrhea. Retroversion after labor is very frequent and every effort should be made to prevent its development. To prevent this patients should avoid strain, and during labor the attendant should avoid severe pressure on the fundus. During the puerperal period the patient should be encouraged to turn frequently in bed. The patient is also advised to lie upon the abdomen whenever she can. A vaginal examination is made about two weeks after labor, and if backward displacement of the uterus is found the knee-chest posture is ordered and later the womb is put in position and a suitable pessary is introduced. The longer the patient has had this complication the greater the chance of relief by surgical interference.

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**Treatment of Retention of the Placenta.**—BASSEWITZ (*Semana Med.*, 1918, No. 25, p. 85) reports 2 cases in which he tried the new method of hydraulic separation of the placenta introduced by Gabaston. The method consisted in injecting into the placenta by the umbilical vein, sterilized salt solution sufficient in quantity to distend the placenta and the excess fluid forms a retroplacental hydroma. This greatly facilitates the delivery of the placenta. In the first case the placenta was expelled, its fetal face presenting, in five minutes; in the second case it was necessary to remove the placenta by the hand. When the uterus is in a condition of inertia or when there are adhesions between the placenta and uterus this method seems a good one. It is not reliable in cases of partial lateral detachment of the placenta. Should the placenta be inverted or attached over the point of entrance of the Fallopian tube the method may cause serious complications.

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**Joined Twins.**—SALMOND (*Lancet*, 1918, No. 194, p. 295) reports the case of a monster child born to parents natives of Natal. The mother had previously given birth to two healthy children and was aged twenty-seven years. In the delivery of the child there was no complication and no physician attended her. When seven days old the monster was seen and successfully photographed; it died on the next day. Both bodies were female and presented normal external genital organs, but urine was passed from only one; there were two anal openings, but the contents of the bowel escaped from only one. The two joined children took food separately and cried without reference to other, so one would remain awake while the other slept. The two hearts did not beat synchronously and respiration was independent in each child. There was but one umbilical cord. There was normal movements of four arms and two legs; there was one limb formed by two fused legs and on the leg were nine toes. At the ankle- and knee-joints there was not much evidence of movement, which was absent at the hip. The skeleton of the child could not be obtained for examination.

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**Dangers of Pituitrin.**—MARCHAND (*Bull. Med. Assn., of Puerto Rico*, San Juan, March, 1918, No. 118, p. 14), states that midwives have learned the action of pituitrin and often use it indiscriminately;



severe lacerations are caused and one case is described in which four injections had been given; when the physician was summoned the patient was moribund, lying in a pool of blood, with the inverted uterus entirely expelled from the body. A similar condition was present in another case, but the uterus was reduced, which was followed by violent bleeding. This patient, a primipara, had received three injections when dilation had scarcely begun.

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**The Blood in Eclampsia.**—SLEMMONS (*Am. Jour. Obst.*, May, 1918) has examined the blood of eclamptic cases. He finds that the analysis in eclampsia and auto-intoxication shows a normal quantity of amino-acids and a slight reduction of nitrogen waste products as urea and uric acid. There is an increase of the sugar in the blood after convulsion, but the total fat is approximately the same in toxemia and normal pregnancy. Cholesterol is increased in eclampsia and lecithin is diminished. The number of the blood plasma and combined carbon dioxide is reduced in normal pregnancy, which would indicate a mild acidosis, and the variations met with in auto-intoxication are insignificant. The results of blood analysis do not support the acid hypothesis nor the derangement of protein metabolism hypothesis of eclampsia, and indicate that the cause of the disease must be sought elsewhere.

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**Surgical Conditions Complicating Extrauterine Pregnancy.**—MUSSEY (*Am. Jour. Obst.*, May, 1918) gives statistics upon this subject from the Mayo Clinic. From 1914 to 1916 inclusive there were more than 10,000 abdominal operations upon women at the Mayo Clinic, and among these 253 pregnant women were found to have definite surgical lesions not dependent on although associated with the pregnancy. Of these, 138 were advised to have operations and 123 were operated on. Sixteen patients went to operation with pregnancies which had not been diagnosticated; one of these was three months advanced, but most of them were under two months. During the same period there were 130 pregnant women with surgical complications who did not come to operation; in 56 of this group the pregnancy was under three months, 61 between three and five and in 13 more than five months. Appendicitis in pregnancy is a frequent occurrence and to be dreaded because of its danger to mother and child. More than 2 per cent. of all pregnant women have appendicitis. An acute attack of appendicitis during pregnancy calls more strongly for operation than does an attack in non-pregnant patients, as the danger of abortion of general peritonitis or rupture of the appendix is greatly increased. In 100 cases there were 9 miscarriages, 2 of which were terminal events from other causes. It may be stated that in general practice every fifth or sixth pregnancy in private practice ends in abortion. In the series quoted there were 1 abortion after appendectomy, 1 after operation for appendix and gall-bladder, 3 after single oöphorectomy and appendectomy, 1 each for enucleation of uterine fibroid tumor and removal of the thyroid gland and 2 following operation upon the gall-bladder and appendix; 4 of these abortions occurred under two months, 2 at two months, 2 at three months and 1 at four months. In the 50 patients operated on within three months' gestation there were 14 miscarriages, or 45 per cent.; between three and five months, 4.4 per cent. There were 5

pregnancies of more than six months in which there were no abortions. The complication in pregnancy second in frequency to appendicitis is inflammation of the gall-bladder, of 2215 women having gall-bladder operations during the period mentioned 26.17 per cent. were pregnant. Those patients having gall-stones or gall-stone pain which are not presenting dangerous symptoms should not be operated upon during pregnancy. In the 26 gall-stone operations there were two deaths and one miscarriage. Pelvic tumor is an important surgical complication of which there were 8 associated with pregnancy and 18 in the patients not operated on. Fibroid tumors not presenting appreciable symptoms, and in such a position as not to obstruct the birth canal at the time of delivery, should not be disturbed during pregnancy. Myomectomy in pregnancy is a dangerous operation. Of the 20 patients with fibroid complicating pregnancy examined in the Mayo Clinic in three years, but 3 were operated on; 1 of these had an abortion. Ovarian tumors complicating pregnancy are very important because they may give rise to a dangerous condition through twisting of the pedicle or rupture of the cyst and obstructing delivery. In the 253 cases in the Mayo Clinic were 6 ovarian tumors, of whom 5 were operated on; in each case a single ovary was removed, in 1 case there had been an ovarian abscess and infection of the tube, abortion followed in this case as in 2 other cases. In 1 case a diagnosis had been made of pregnancy associated with a large uterine fibroid but the patient was found to have an ovarian cyst eight weeks after a normal delivery. Other operations were amputation of the breasts, nephrectomy, removal of hemorrhoids, partial removal of the thyroid and in 1 case an operation on the cervix; this patient was sent with a diagnosis of sterility having apparently menstruated normally three and a half weeks before; pregnancy was not interrupted and the patient went on to normal delivery. There were 2 radial amputations of the breasts for carcinoma, 1 six and a half months and 1 seven months pregnant, without interrupting the pregnancy. In 3 other cases adenoma was removed from the breast; none of these had abortion. In 1 case a tuberculous kidney was removed without interrupting pregnancy; 35 pregnant women with adenoma of the thyroid were examined and 31 advised to delay operation until after confinement; 6 patients having exophthalmic goitre were pregnant, of whom 4 were operated on, but in only 1 a primary thyroidectomy done. There were 1055 women having exophthalmic goitre, of whom about 0.5 per cent. were pregnant, of 2404 women with simple goitre only 1.4 per cent. were pregnant. The writer concludes that the operation that can be postponed until after confinement should not be done during pregnancy; when necessary the appendix can be removed during pregnancy without undue risk to mother and child. It is not often necessary to operate on fibroid tumor complicating pregnancy, but when necessity arises there is but little risk. It is safer to remove an ovarian cyst complicating pregnancy than to allow it to go on. It is thought to be more favorable if operation is performed in the first half of pregnancy, but should necessity arise it may be done in the second half as well. In the experience of the reviewer pregnancy and parturition are especially liable to cause chronic appendicitis to become acute, hence the appendix should be removed in all pregnant women so soon as the diagnosis of appendicitis is made. Operations upon the

kidney, in the experience of the reviewer, have been limited to drainage but this has been successful without the interruption of pregnancy. In one case of colon bacillus infection he removed the appendix and drained the kidney at the same time without interrupting pregnancy and the patient made a good recovery. Infection of the gall-bladder is far from uncommon among pregnant women, and it is the opinion of the reviewer that such cases should be operated on so soon as pregnancy is over provided they do not become acute, in the presence of acute and severe infections there can be no question about the necessity of immediate operation.

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**Gall-bladder Disease Complicating Pregnancy.**—WHITE (*Am. Jour. Obst.*, May, 1918) reports the case of a woman, aged twenty-two years, who had been operated on twice because of gall-stones and jaundice. Five years later she was admitted to the hospital, supposedly in labor. She had suffered from persistent vomiting during the greater part of pregnancy, and six weeks before admission she began to have pain in the region of the gall-bladder and was jaundiced. On examination the uterus was enlarged to full term; fetal movements could be felt and the fetal heart could be heard. There was marked tenderness over the gall-bladder, and on vaginal examination the cervix was long, hard and undilated. The patient was not in labor and her pain was evidently caused by some condition in the gall-bladder. At the end twenty-four hours the patient was much worse, and it was decided to empty the uterus first by abdominal section and then to explore the gall-bladder. On section the uterus contracted with difficulty and the child was stillborn. The gall-bladder was found much enlarged, with many adhesions, and contained mucopurulent bile; no stones were discovered. A drainage tube was sutured in the gall-bladder and the drainage of bile persisted for twenty-nine days. The wound was entirely closed at the end of thirty-five days, the patient making a good recovery. A pure culture of *Bacillus pyocyaneus* was obtained from the contents of the gall-bladder.

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## GYNECOLOGY

UNDER THE CHARGE OF

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**Absorption of Drugs and Poisons through the Vagina.**—As a war time contribution which may assist in the lowering of both maternal and infant mortality, MACHT (*Jour. Pharm. and Exp. Therap.*, 1918, x, 509) has been carrying on a series of investigations in the pharmacological laboratory at Johns Hopkins University on the absorption of drugs and poisons through the vagina and has reached the following conclusions: (1) It has been shown that a large number of drugs and poisons—alkaloids, inorganic salts, esters and antiseptics—can be and are easily absorbed through the vaginal wall. (2) Such absorption can be demon-

strated experimentally by physiological and chemical means. (3) A review of the clinical and toxicological literature shows that poisoning through the vagina, of a grave character, is not very rare. (4) The experiments indicate, on the one hand, the possibility of administering drugs therapeutically for their constitutional effects, through the vaginal route; and on the other hand, emphasize the great danger of the indiscriminate employment of various poisonous substances in the form of douches, tampons, "uterine wafers," etc. The investigations were carried out upon cats and dogs. In some cases the substances were identified by chemical means after their absorption, in some the pharmacodynamic and toxicological effects were taken as proof of the action of the substances upon the body, and in other cases, both physiological and chemical evidence could be obtained.

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**Repair of Complete Rectovaginal Lacerations.**—HAYNES (*Ann. of Surg.*, 1918, lxxvii, 501) has recently described an operation which he performed in January, 1916, for the repair of a total division of the rectovaginal septum from the cervix to and through the perineum. While his method is very similar to that described by Lignen in 1903 for the treatment of high rectovaginal fistula, the literature on the treatment of complete rectovaginal lacerations is so scanty that the steps of Haynes's operation, which are essentially as follows, deserve our attention: (1) Begin the separation of the rectum from the vagina just above the levatores ani and in the space between the rectovaginal fascia and the rectum. (2) Separate the bowel downward through the anal canal and cut through the mucocutaneous junction. Carry the mobilization of the bowel upward high enough to obtain sufficient sound rectum so that the undamaged rectum may be drawn beyond the level of the skin. (3) Divide the anococcygeal tissues sufficiently far toward the coccyx to permit suturing the retracted sphincter ani externus in front of the rectum. (4) Rotate the rectum through 90 degrees and suture it in place, especially reforming the attachments of the levatores ani to the bowel. Trim off the excess of rectal tissue and suture the skin to the rectal mucosa. Drain the region behind the rectum. (5) Complete the operation by a perineorrhaphy.

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**Preliminary Report of an Operation for Cystocele.**—RAWLS (*Am. Jour. Obst.*, 1918, lxxvii, 359) has elaborated a technic for operation upon cystoceles which, he feels, promises to restore the anatomical relations in the bladder and to prevent the many abnormal conditions which frequently result as the after-effects of cystocele operations by offering a strong and anatomical restoration of the supports of the bladder without causing anteroposterior shortening of the anterior wall of the vagina. His method may be used in all forms of cystocele, but in cases with complete prolapse of the uterus, other additional methods are required to relieve injury to the posterior segment of the "holding apparatus" and the injury to the "supporting apparatus." The technic of Rawls's operation is as follows: A small volsellum forceps is applied to the mucous membrane of the anterior vaginal wall about 1 cm. above the cervix and another forceps about 1 cm. below the external urethral orifice. Between these forceps a vertical incision is made through the mucosa and superficially into the underlying tissues. These cut edges

are retracted and the incision carried forward until the midportion of the bladder is reached. It is then continued downward until the cervical attachment of the bladder pillars and the so-called uterovesical ligament are demonstrated. The latter is cut with scissors, keeping well in midline in order to avoid severing any of the cervical attachments of the bladder pillars. The bladder is next separated by blunt dissection as far up as its peritoneal reflexion from the cervix and well out to either side, care being taken to free it from the underlying pillars upward to the urethra. If there is an urethrocele the dissection is carried up to the external urethral orifice. When the bladder is well mobilized its pillars are dissected from the underlying vaginal mucosa. The next step must be done carefully in order to avoid destroying or buttonholing the fascial sling. With a finger under the mucosa as a guide, the thinned-out fascial edge is dissected with a knife from the underlying mucosa. The mucosa flap is made paper-thin and forceps are applied as tractors to the fascial and mucosal edges. This cutting dissection is continued from the midline, downward and upward for a short distance laterally until a distinct line of cleavage can be demonstrated the whole length of the primary incision, after which further separation by blunt dissection is secured from the overlying pillars well out on either side to the "arcus tendineus." The bladder and its true lateral ligaments are now freely mobilized and the latter are overlapped from side to side by transverse mattress sutures of kangaroo tendon, one or two sutures entering the cervical tissue at the level of the internal os. These sutures prevent anteroposterior shortening of the anterior vaginal wall and draw the underlying fascia smoothly under the overlapping fascia. The cervical suture reattaches the fascia to its original place on the cervix and forms a shelf on which the bladder rests. The free edge of the overlapping fascia is then closed over the underlapped fascia by interrupted kangaroo tendon sutures. The thin vaginal mucosa flap is now excised for a short distance on either side and its edges approximated in midline by interrupted chromic catgut.

**Cystoscopic Study of the End-results of Various Forms of Cystocele Operation.**—The condition of the interior of the bladder after cystocele operations has never been given special consideration, attention having been centered principally on restoring the anterior vaginal wall to an apparently normal state by an operation which would insure a permanent result. The interior of the bladder must necessarily be very tolerant, since symptoms seldom develop until infection has occurred, even though, as has been found by BROWN and RAWLS (*Surg., Gynec., Obst.*, 1918, xxvi, 502) in their recent cystoscopic studies, the base of the bladder is thrown into folds and sulci in most instances after cystocele operations. The question naturally arises as to whether such a condition does not render more possible some after disturbance of a systemic character. In their cystoscopic studies, the authors have noted that the kind of operation seemed to have no effect upon the degree of distortion of the base of the bladder. In anchoring the bladder base to a higher plane with sutures, attaching it to the broad ligament, proportionately as many abnormalities were produced as by the other method of leaving the bladder free after its separation from the uterus and bringing together the tissues underneath it. The ideal operation should not only

provide a permanent vaginal restoration of the prolapsed anterior wall, but should also leave the base of the bladder in the normal plane. The authors believe it is the degree of anterior prolapse which decides whether the base of the bladder is left in a normal or convoluted state. Patients with only a moderate prolapse, upon whom a small area of separation of the mucosa was done, seemed less susceptible to extensive folding of the base than those with an extensive prolapse and proportionately larger separation. Rawls is of the opinion that if due care is exercised in preserving the fascial pillars of the bladder when separating the vaginal mucosa, and equal attention is devoted to freeing the bladder from these pillars and from its uterine attachment, equally good results will be obtained in all degrees of cystocele, not only as to the vaginal aspect, but also in a minimum of folding of the base of the bladder, if not its complete absence.

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**Treatment of Cystocele and Uterine Prolapse during the Child-bearing Period.**—According to WATKINS (*Surg., Gynec., Obst.*, 1918, xxvi, 570) the essential features of such an operation are wide incision anterior to the cervix, free separation of the herniated part of the bladder, closure of the hernial opening by circular sutures, restoration and fixation of the urethrocele and perineorrhaphy, while amputation of the cervix, trachelorrhaphy, plastic surgery on the broad ligaments and vaginal fixation are adjuncts which may be frequently utilized. The following are the procedures, as outlined by Watkins, to be used singly or collectively, according to the needs of the case: **Transverse Incision:** The transverse incision in front of the cervix should extend freely across the anterior vaginal wall to permit the cervix to tilt easily upward and backward as the operation progresses. This lengthens the anterior vaginal wall and allows the body of the uterus to drop forward without undue flexure. The anterior vaginal wall is often congenitally or otherwise shortened in these cases. **Separation of the Anterior Vaginal Wall from the Bladder:** Blunt dissection with Mayo scissors saves time and lessens bleeding and traumatism if care is taken to find the plane of fascia between the vagina and bladder. The width of separation varies. It should not be wide enough to endanger the ureters or injure large veins, yet should include all redundant mucous membrane and should permit complete separation of the herniated part of the bladder. **Separation of the Bladder from the Cervix:** This is also most satisfactorily done with scissors if caution is taken to find the dividing plane of fascia. The herniated portion of the bladder should now be completely freed from the sac. The peritoneum is incised if the cystocele is large, if intraperitoneal exploration is desired, if the uterus is retrodisplaced, or if vaginal fixation of the round ligaments is contemplated. At this time amputation of the cervix, if indicated, is done. Watkins believes in amputation in occasional cases of excessive elongation of the cervix only, because it endangers labor and stenosis. **Plastic Operations upon the Broad Ligaments:** Plastic operations on the broad ligaments are a valuable adjunct to the operation, if the uterus is much prolapsed, much increased in size, or if the anterior vaginal wall is much shortened. **Vaginal Fixation of the Round Ligaments:** The technic is much the same as that formerly employed in the treatment of retropositions of the uterus. It is especially valuable when the prolapse is complicated by

backward displacement of the uterus. It is also of great value in cases of extensive prolapse of the uterus. It adds materially to our ability to cure some of the very bad cases without subjecting them to operations to produce sterility. The round ligaments are not long enough for vaginal fixation without undue tension, except when the uterus is retro-displaced or much prolapsed. The ligaments should be firmly fixed to the submucous connective tissue by interrupted, buried, fine linen or silk suture at a place in the vaginal wall that will restore and fix the urethrocele, which is almost invariably present, to its normal location. The point of fixation will be further considered later. Advancement of the Anterior Vaginal Wall upon the Uterus: This consists in changing the place of attachment of the vaginal wall to the uterus to a plane higher on the uterus than formerly occupied, as devised by Goffe. The more the vaginal wall is advanced upon the uterus the more certain must be the cure of the bladder and uterine displacements, but because of the possible complication of pregnancy and labor it is not safe to attach the vagina much higher than the anterior reflexion of the peritoneum. Excision of the Vaginal Flaps: Redundant tissue should be excised to an extent consistent with minimum tension upon sutures. The hypertrophied mucosa (skin-like tissue) which is generally present over the base of the urethra should be excised, otherwise it is liable to protrude later. Sutures: Interrupted, buried, fine linen or silk sutures are advocated for the broad ligament, for suture of loops of the round ligaments, and in exceptional cases two or three such sutures may be needed in the connective tissue; otherwise interrupted or continuous Claudius catgut should be used entirely. The part of the wound caused by excision of the hypertrophied mucosa over the base of the urethra should be closed first. The placing of the first "circular" suture is highly important, as it determines the places the urethra will be left in, it closes all or most of the hernial opening of the cystocele, and it should ensure an anterior position of the uterus. It should include the vaginal wall, so that when tied it will restore the urethra to its normal location, which is one of relative fixation. The suture should pass through the anterior surface of the uterus at a place above its point of pivotal action when tipped forward or backward, so that when tied it keeps the body anteriorly. When tied care should be taken not to include a knuckle of the bladder. Succeeding sutures should parallel this one at short distances until the wound is closed.

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## PATHOLOGY AND BACTERIOLOGY

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**Inquiry into the Presence of Diphtheria and Diphtheroid Organisms in Open Wounds.**—In September, 1917, a report was published by Fitzgerald and Robertson upon the presence of the diphtheria

bacillus in the wounds of returned soldiers. These observations were made in Canada upon soldiers returned from the hospitals in England. The authors found no less than 40 out of 67 cases yielded cultures of *B. diphtheriæ*. These rather startling findings led to an investigation by ADAMI, BOWMAN and others (*Canadian Med. Assn., Jour.*, 1918, viii, 769) of wounds in the hospitals in England. These authors made a thorough investigation of possible carriers among the patients and hospital personnel. Cultures were made from wounds with a particular attempt of isolating members of the diphtheria and diphtheroid groups. Organisms showing characteristic morphology were tested on differential media and such organisms presenting cultural characteristics of *B. diphtheriæ* were tested for pathogenicity upon guinea-pigs. Of this study 306 cases were examined. Of these 56 showed the presence of diphtheroid organisms while 2 contained bacteria yielding all the characteristics of the *B. diphtheriæ*. Two other organisms which showed morphological and cultural characteristics of the bacillus of diphtheria were found to have no pathogenic qualities when tested upon animals. The authors conclude that diphtheroid organisms resembling *B. diphtheriæ* are present in a certain percentage of wounds. These organisms must be distinguished from the toxin producing bacteria by animal experiment. They indicate that the cultural responses upon the sugar media are in themselves not sufficiently indicative of the true nature of the *B. diphtheriæ*. The authors are not able to substantiate the claims of Fitzgerald and Robertson on the high incidence of *B. diphtheriæ* in the wounds. Diphtheroid organisms, on the other hand, were found in almost 20 per cent. of the cases.

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**Bacteriological Examination for Meningococcus Carriers.**—A recent examination of all students and officers in the Kansas State Agricultural College to determine carriers of the meningococcus has led to a description of the technic employed with special emphasis on certain points. BUSHNELL (*Jour. Med. Res.*, 1918, xxxviii, 1) reports excellent results obtained by careful handling of technical methods already in use in most laboratories. By a laboratory force of seven workers, 500 examinations were made daily. Swabs were plated immediately, on a medium consisting of 2 per cent. meat infusion agar to which had been added 1 per cent. peptone, 0.5 per cent. glucose and 5 per cent. defibrinated sheep's blood. These were incubated for twenty-four to forty hours and colonies examined by a slightly modified Gram stain. The author emphasizes the importance of planting cultures immediately to ensure a rapid and abundant growth of the meningococcus. Plates were warmed before using. Another point he emphasizes is the streaking of each swab toward the center of the plate by means of a platinum wire, as the growth of the meningococcus is easily prevented by many other types of microorganisms. The West tube was found to be of little value for this work. It is not only expensive and difficult to make, but it is useless to anyone experienced in taking swabbings from the nasopharynx. There is greater tendency to gag the patient by the use of the tube, and frequently a great deal of mucus obtained in the swabbing is removed on the inside of the tube when the swab is drawn out. Much more accurate results were obtained by rapid implantation on



fresh warm plates. By these improved methods of technic it was found that 2.52 per cent. of the normal population of the community were meningococcus carriers, many of whom were workmen or soldiers from Camp Funston. None of them developed the disease and all were eventually made free from the carrier state.

**Influence of Parathyroidectomy on the Gastro-intestinal Mucosa of Dogs and Rabbits.**—In an earlier series of experiments the author, FRIEDMAN (*Jour. Med. Res.*, 1918, xxxviii, 69) observed the development of intestinal lesions following partial removal of the thyroid. Similar observations have been recorded by Carlson and Jacobson. In the present study the author repeated his experiments in removing a portion of the thyroid from ten rabbits and ten dogs. In addition to this the complete extirpation of the thyroid was performed upon other animals. The author claims that in performing these operations one or more of the parathyroids were left in the majority of animals. The animals were killed from four to one hundred and twenty-four days after operation. At autopsy observations were made respecting the size of the hypophysis, adrenals and remaining lobe of the thyroid. In the gastro-intestinal canal erosions and ulcers were found in the stomach, duodenum and occasionally in the appendix. Gastric or duodenal lesions were found in eleven out of fourteen dogs while the appendix was involved only twice. A very similar percentage was obtained in the rabbits. In his discussion the author associates the gastro-intestinal lesions with the operative procedure, the exact nature of which is difficult to interpret from the author's own description. The nature of the lesions in the gastro-intestinal tract is not described, and although he states that "the picture did not correspond to chronic peptic ulcer in man," he draws conclusions suggesting their identity. The analysis of the experimental work is far from conclusive, particularly in indicating the influence of derangements of the thyroid or parathyroid upon the tissues of the gastro-intestinal canal.

**Researches of Cancerous Diseases in Norway.**—GADE (*Jour. Cancer Res.*, 1918, iii, 107) had at his disposal for study of cancer in Norway the statistics compiled by the Norway Committee for Cancer Research for the years 1908–1912 and the Official Mortality Reports during the years 1902–1911. From these latter a survey of geographical distribution and general frequency of malignant tumors was obtained. While a marked continuous rise in the number of deaths each year from cancer occurs there are several factors which considerably diminish the apparent increase. Thus when the corresponding growth in the population and better diagnosis of the disease have been taken into consideration the real increase does not exceed the ratio of 1 to 1.6. The death-rate of 10.6 per 10,000 (cancer figure) is estimated to be fairly evenly distributed between city and urban population. However, wide variations in the number of cancer deaths exist in different districts, and especially conspicuous is the high rate found in certain densely populated localities. An attempt was made to determine whether a parallelism existed between percentage of cancer deaths and that of aged persons in certain districts (age figure), but although a certain coincidence between low or high age and cancer figures could be noted no

ruling law could be definitely demonstrated. It was noted that in many small towns on the south coast where old sailors resided the cancer mortality was exceedingly high. The relation of cancer to age is similar to that generally found, namely, a gradual increase in frequency through every decennium and reaching an absolute maximum between sixty and seventy years. The figures are very equally distributed between the sexes, when all ages are taken into account, though above thirty-five years a preponderance occurs among males. The most noteworthy feature regarding location in organs is the predominance of gastric carcinoma, which represents 61.2 per cent. of the whole number, with a greater prevalence of the disease in the male sex. The material collected by the Norwegian Cancer Committee is dependent upon voluntary contributions from practitioners, and consists of only 4219 cases. Comparison of this material with the official mortality statistics reveal one striking feature which they possess in common, namely, the predominance of cancer of the stomach. Conspicuous among these cases is also the preponderance of malignant tumors in advanced age. More than one-half the cases reported occur between fifty and seventy years. In 2554 cases a study regarding the distribution of cancer according to occupation was made. Although this number is comparatively small it is interesting to note that the high number (1034) of cases occur in farmers and over 800 cases in factory employees and skilled laborers. Of the cases reported 2706 give information regarding heredity, concerning which the author concludes there is no data to support the supposition of direct transfer from one individual to another. Thus in 304 families, numbering 677 patients, the identical localization occurs in parent and offspring, though in the majority of cases the stomach is the site involved. This, however, may be merely a coincidence, since in 417 families embracing 883 cancerous individuals the localizations were most varying. The author suggests "that some of the cases reported point to a direction of family disposition, possibly in the shape of an inherited tendency toward fatal dislocations in the sense of Cohnheim."

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**Fluctuations in the Growth Energy of Malignant Tumors in Man with Special Reference to Spontaneous Recession.**—Among investigators of transplanted tumors in animals it is a well-recognized fact that retrogressions not infrequently occur. Clinicians have also reported instances of similar recessions of tumor in man, and it has even been estimated that complete retrogressions occur once in every 100,000 cases. These retrogressive changes may vary from a temporary standstill to complete disappearance of the growth; they may be of epithelial or connective-tissue origin and widely distributed in the body, and they may occur at any age or in either sex. Thus far it has not been possible to determine any one specific factor responsible for these variations. Indeed, they apparently are accompanied by the most diverse physiological conditions. With a view to an analysis of this phenomenon of recession in tumor growth from the standpoint of our present knowledge of experimental cancer ROHDENBURG (*Jour. Cancer Res.*, 1918, iii, 193) has gathered from the literature 302 cases of marked recessions or spontaneous cures, which he has divided into three groups, depending upon the efficiency of the diagnosis. Group I consists of those reports

which stand a most rigid scrutiny; group II contains those cases in which some slight question might be raised regarding adequate control of possible diagnostic errors; group III comprises those cases open to more or less grave doubt as to diagnosis. Each group is again subdivided into complete and partial retrogressions. The growths vary widely in type, but malignant epithelial tumors are present in the largest number. The causes of retrogression reported are varied, incomplete operation and heat being about evenly divided. In many cases rise of temperature immediately follows the operation for removal of the mass. The heat may be applied externally or it may be due to an infection such as erysipelas, tuberculosis or pneumonia. A continuous temperature of  $104^{\circ}$  to  $105^{\circ}$  for several days is most effective. Less frequently some profound change in the metabolic processes of the individual, *e. g.*, cachexia or puerperium, is assigned as the cause of the retrogression. In a number of cases simple exploratory laparotomy was sufficient to cause retrogressions, which occasionally resulted in a complete disappearance of the tumor. Why such a procedure should effect a cure remains at present quite inexplicable.

**Examination of Blood Preliminary to the Operation of Blood Transfusion.**—Although there has been a gradual improvement in the technic of the methods used for testing the incompatibility of bloods previous to transfusion even the more recent tests require the withdrawal of a considerable quantity of blood from both patient and donor. The method outlined by Coca (*Jour. Immunol.*, 1918, iii, 93) permits the mutual tests to be made with practically a drop of blood from each individual. Further, only a few glass slides and a blood-mixing pipette, such as is used in making a leukocyte count, is necessary. By the use of the stem of the pipette, which is graduated into ten divisions, a dilution of the blood of both donor and patient can readily be made in the proportions of 9 parts of blood to 1 part of diluent. In order to prevent clotting the pipette is previously rinsed with 10 per cent. sodium citrate, of which a sufficient amount is left in the pipette to fill the lowest division. Blood is then sucked up to the point on the stem marked 1. The two samples of citrated blood are blown out upon glass slides, and from these preliminary dilutions second mixtures of blood in the proportions of 1 to 10 can be made with normal saline by adding to 9 parts of the saline 1 part of the citrated blood. These two procedures give 10 to 1 and 1 to 10 dilutions of both donor and patient's blood, from which the combination requisite for testing for agglutination can be readily made. Thus, three divisions each of citrate blood of donor and patient and three divisions of citrate blood of donor to three divisions of saline blood mixture of patient, and *vice versa*. These are examined microscopically for clumping of corpuscles. In actual practice it is not necessary to make the 1 to 10 dilution of the patient's blood in saline because the corpuscular content of the patient's blood is reduced sufficiently to meet the purpose of dilution. If more than one donor is to be tested the slides must be duplicated or triplicated according to the number of perspective donors. When it is desired to perform the indirect test in which both bloods are examined to ascertain in which one of the four agglutinin groups they belong a similar technic is employed, except that each blood is tested against sera, known to belong to group I and II, for evidence of agglutination.

**Studies on the Antitrypsin of Serum.**—In this work FUGIMOTO (*Jour. Immunol.*, 1918, iii, 51) deals with three aspects of antitryptic activity, namely, its inactivation, the part of the serum in which it is found and the nature of the reaction. His experiments were made throughout with the Bergman method, which he modified by reducing the original concentrations of the reagents. To given amounts of casein are added varying quantities of blood serum and the inactivation is indicated by absence of any precipitation on the addition of acetic acid to the mixture. Serum was employed in the concentration of 1 per cent. to avoid heat coagulation of the serum *per se*. The conclusions reached from his experiments on the effect of heat on antitrypsin confirm in general those of the earlier investigators, namely, that the antitrypsin is thermostable and that the point of inactivation varies slightly in various sera. Heating rabbit and sheep sera for ten minutes at 75° C. causes a complete inactivation, while a temperature of 65° C. for the same time suffices when horse serum is tested. In no case was the author able to obtain any diminution of the antitryptic properties of the serum by shaking. In order to test in what part of the blood the antitrypsin is found, serum was fractioned by several methods in globulin and albumin and the antitryptic activity of each fraction noted. It was demonstrated that the antitryptic action occurs in both fractions, but in a less degree in the albumin, as was previously stated by Döblin and Kammerer. It was further demonstrated that the antitrypsin is not lost from either the globulin or albumin by dialysis and that the ether extract of serum does not contain antitrypsin. An interesting observation deals with the possible identity of antitrypsin and serum albumin. Purified crystallized serum albumin was shown to exert an antitryptic action, but whether the serum albumin alone is responsible for this activity was not demonstrated.

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## HYGIENE AND PUBLIC HEALTH

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UNDER THE CHARGE OF

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**Germicidal Action of Freezing Temperatures upon Bacteria.**—HILLARD and DAVIS (*Jour. Bacteriol.*, July, 1918) state that intermittent freezing of bacteria exerts a more effective germicidal action than continuous freezing. The reduction is much less in milk and cream than in pure tap water when freezing temperatures are applied, due, no doubt, to physical protection offered to the bacteria by the colloidal and solid matter in suspension. The degree of cold below freezing is not a very important factor in the destruction of bacteria. There is no critical

temperature below freezing when the germicidal effect is greatly accelerated. The death-rate of *B. coli* is much higher in media which are frozen solid than it is in the same media not solid and at a slightly lower temperature. Crystallization, probably resulting in mechanical crushing, is an important germicidal factor in causing the death of bacteria at zero degrees Centigrade and below. The greatest reduction occurs promptly upon freezing and refreezing, but is not caused so much by the sudden change in temperature as by this mechanical factor.

**Scabies in Military and Civil Life.**—KNOWLES (*Jour. Am. Med. Assn.*, November 16, 1918) states that scabies should be treated by the routine suggested by the leading dermatologists of Great Britain, France and the United States, which is as follows: On the first day the patient is given a warm bath with plenty of soap. One rubbing is given with sulphur (precipitated sulphur, 1 dram to the ounce of petrolatum). On each of the next three days a sulphur rubbing is given. On the fifth day a warm bath, with plenty of soap, and clean clothes are given. Thorough and minute examination of the entire body is made to ensure that no active disease remains. If active lesions are still present four more days of sulphur rubbings are given, followed by another warm bath, another careful examination of the skin surface and clean clothes. The disease is a greater problem in military than civil life, because of its greater frequency and severity. It is rather atypical in military life because of the comparative freedom of the hands and more marked involvement of the penis. Complications secondary to scabies are much more frequent and markedly more severe in military than in civil practice. A rather prolonged convalescence is observed in approximately 10 per cent. of scabies in military practice.

**New Pathology of Syphilis.**—WARTHIN (*Am. Jour. Syphilis*, July, 1918, No. 3, ii) states that the gumma is not the essential typical lesion of old or latent syphilis. It is a relatively rare formation, and the great majority of cases of syphilis run their course without the formation of gummatous granulomata. The new pathology of syphilis is based upon the demonstration that the essential tissue lesion of either late or latent syphilis is an irritative or inflammatory process, usually mild in degree, characterized by lymphocytic and plasma-cell infiltrations in the stroma, particularly about the bloodvessels and lymphatics, slight tissue proliferations, eventually fibrosis and atrophy or degeneration of the parenchyma. These mild inflammatory reactions are due to the localization in the tissues of relatively avirulent spirochetes. Syphilitic inflammations of this type occur in all tissues and organs, but are most easily recognized in the nervous system, heart, aorta, pancreas, adrenals and testes. They are, however, usually widely distributed throughout the entire body, although in individual cases showing special predilection for certain organs or tissues. No explanation of these system, organ or tissue predilections is yet evident; neither is there any explanation of those cases in which all organs and tissues show the most severe degree of these lesions. The syphilitic is a spirochete carrier. In this respect the *Spirocheta pallida* is to be classed with the trypanosome, the malarial organisms, lepra and tubercle bacilli, streptococcus, etc. Syphilis tends to become a mild process,

but at any time the partnership between the body and the spirochete may become disturbed and tissue susceptibility or virulence of the spirochete become increased so that the disease again appears above the clinical horizon. Immunity in syphilis depends upon the carrying of the spirochete. A price is paid for this immunity in the form of the defensive inflammatory lesions previously described. The disastrous effects of syphilitic infection usually require a period of years for their development. The slowly progressive lesions, fibrosis and atrophy, may at last manifest themselves in paresis, tabes, myocarditis, aortitis, aneurysm, diabetes, hepatitis or in many other forms of tissue damage and functional disturbance. Lesions of the viscera are much more common and important clinically than those of the central nervous system, but they are rarely recognized as syphilitic by the clinician. Syphilitic death occurs most frequently in males between the ages of forty and sixty. Chronic myocarditis is the most common form of death due to syphilis. The pathological diagnosis of syphilis is essentially microscopic. Only in a relatively small number of cases are the gross lesions (tabes, gumma, aortitis, etc.) typical enough to be recognized by the naked eye. A negative diagnosis of syphilis cannot be given with any certainty without a routine microscopic examination of all organs and tissues, but particularly of the left ventricle wall, the aorta, both its arch and abdominal portion, the testes, pancreas and adrenals.

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**Tuberculosis and Syphilis.**—ADELUNG (*Jour. Am. Med. Assn.*, April 27, 1918, No. 17, lxx, 1211) states that in order to impress the importance of the use of the Wassermann test in tuberculosis patients the cases in the Alameda County Tuberculosis Clinic during the past four years were studied. The Wassermann tests were made at the State Hygienic Laboratory in Berkeley. In all cases the sputum examinations confirmed the diagnosis of tuberculosis. Four years are included, 1914 to 1917, during which 195 cases received Wassermann tests. Summing them up for the four years, in 17, or 8.7 per cent., the reaction was positive. This represents what would have been overlooked by the average practitioner when treating open cases of tuberculosis of the lungs without making the Wassermann test.

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**Toxic Jaundice Due to Dinitrophenol.**—WARTHIN (*Int. Assn. of Med. Museums*, Bulletin No. vii, May, 1918) states that poisoning by dinitrophenol is not mentioned by either Thompson or Oliver. Dr. Alice Hamilton, likewise, does not mention it in the Government Bulletin of occupational poisoning in munition workers. Warthin found from his observations, however, that it is capable of producing acute yellow atrophy and toxic jaundice, and states that it must be added to the list of dangerous occupational hepatotoxic poisons. At this time it is, therefore, increasingly important that suitable protection be provided for workers with this product in munitions manufacture.

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**Trench Fever.**—The Medical Research Committee of the American Red Cross (Report of Commission, 1918), consisting of Major Richard P. Strong, Major Homer F. Swift, Major Eugene L. Opie, Captain Ward J. MacNeal, Captain Walter Baetjer, Captain A. M. Pappenheimer, Captain A. D. Peacock and Lieutenant David Rapport, studied

the method of transmission of trench fever and reached the following conclusions: (1) That trench fever is a specific infectious disease; that it is not a modified form of typhoid or paratyphoid fever and is not related, from an etiological standpoint, to these diseases. (2) That the organism causing the disease is a resistant filterable virus. (3) That the virus causing trench fever is present particularly in the plasma of the blood of trench fever cases and that such plasma will produce the disease on inoculation into healthy individuals. (4) That the disease is transmitted naturally by the louse *Pediculus humanus*, Linn., var. *corporis*, and that this is the important and common means of transmission. That the louse may transmit the disease by its bite alone, the usual manner of infection, or the disease may be produced artificially by scarifying the skin and rubbing in a small amount of the infected louse excrement. (5) That a man may be entirely free from lice at the time he develops trench fever, the louse that infected him having left him some time previously as its host, and that the louse need only remain upon the individual for a short period of time in order to infect him. (6) That the virus of trench fever is also sometimes present in the urine of trench fever cases and occasionally in the sputum, and that the disease may be produced in man by the introduction of the virus in the urine or sputum through the scarified or otherwise abraded skin. (7) That since the urine and sometimes the sputum of trench fever patients are infective, these should be sterilized in order to avoid the possibility of accidental infection from them. (8) That in order to prevent trench fever or limit its spread, and thus save man-power for the armies, greater efforts must be made to keep soldiers in general from infestation with lice. The authors state that exceedingly great care should be taken to completely disinfect all patients as soon as practicable, and particularly upon their entering the hospital. Patients on entrance should be carefully bathed and subsequently sponged with alcohol. Their clothing and blankets should be removed, and, whether or not lice or ova are found upon them, should be carefully sterilized by moist heat at a temperature not below 70° C. for half an hour, since it is possible for the virus to be still present on the clothing. It should be borne in mind that a man with trench fever may be entirely free from lice at the time that he develops symptoms of the disease. Trench fever patients should at all times be carefully protected from louse infestation, and inspection of them for lice should be made daily. They should be treated in separate wards. As the urine contains the virus and is infective it should be sterilized during the active stages of the disease. Sputum cups should be provided for the patient and any expectorated sputum and saliva from them sterilized. Officers should regard the systematic destruction of lice as one of the most urgent of their duties, and should exercise every effort to prevent louse infestation among soldiers and to see that any of them infested with lice are promptly disinfected and their clothing sterilized. The above precautions are of the utmost importance in order to prevent the further spread of trench fever among troops.

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**Observations on the Presence of the Meningococcus in the Blood.**—MAXCY (*Jour. Infect. Dis.*, November, 1918) made studies upon the epidemiology of epidemic meningitis at Camp Beauregard. He states

that twenty-seven blood cultures done on patients suspected of being cases of abortive meningococcus infection were negative. The abortive meningococcus infection was not a considerable factor in the epidemiology of the disease during the epidemic in February, 1918. The author reports a case of meningococcus infection in which the blood-stream invasion was transient and the organism quickly localized in the meninges, where it yielded to the intraspinal injection of serum; and a case of meningococcus septicemia with transient meningeal involvement, with recovery only after the injection of large amounts of antimeningococcus serum intravenously.

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**Acute Respiratory Diseases among Troops with Special Reference to Empyema.**—BEALS, ZIMMERMAN and MARLOW (*Jour. Infect. Dis.*, November, 1918) in their study of acute respiratory diseases among troops detailed the incidence of various respiratory conditions, measles and rubella in their relation to each other and to the more serious conditions, pneumonia and empyema. They state that respiratory infections in 1917 and 1918 occurred among troops in waves, the greatest severity of the diseases being at the height of each wave. Not only were pneumonia and empyema more frequent and severe, but also tonsillitis, pharyngitis and bronchitis. The control of such epidemics would appear to depend on the sanitation in barracks as regards ventilation; adequate space and proper separation, especially of those even slightly affected with respiratory disease; on line officers not allowing overheated men to stand inactive in cold winds; on not indiscriminately giving triple typhoid inoculations at the very entrance of the soldier to camp without regard to any respiratory infection he might have at the time; on careful attention to overexertion and exposure of soldiers having mild respiratory disease and on close attention to the details of equipment to ensure adequate clothing for the unacclimated raw recruit on his arrival.

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**Survival of Typhoid Bacilli in Sour Milk.**—MARSH (*Am. Jour. Public Health*, August, 1918, p. 590) states that typhoid and paratyphoid bacilli disappear from souring milk with an acidity represented by about 4 c.c. of  $\frac{N}{10}$  NaOH. The dysentery bacilli are more sensitive, disappearing one day earlier than the others. The tests indicate that *B. typhosus* is sensitive to acidity and is usually destroyed in milk in a short time at about the degree of acidity occurring in fresh buttermilk as obtained in the New York market. Buttermilk would seem to be free of danger as a means of distributing *B. typhosus* or *B. dysenteriae* in the ordinary course of events.

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ORIGINAL ARTICLES

CLINICAL STUDIES IN CUTANEOUS ASPECTS OF  
TUBERCULOSIS.

I. "TUBERCULOUS" PURPURA, ERYTHEMA MULTIFORME AND  
ERYTHEMA NODOSUM.

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THE tendency of recent advances in the study of the etiology of dermatoses has been, increasingly, to show that many supposed clinical entities, so styled on purely morphological grounds, have a multiple etiology. One of the conditions undergoing such etiological revision is the erythema group, including the clinical entities of erythema multiforme and erythema nodosum. The work of revising our outlook on erythema multiforme, purpura and urticaria was well begun by Osler in 1895. Erythema nodosum is of particular interest because on its border lie erythema induratum and the group of dermatoses designated after Darier as "tuberculids," whose intimate relation to tuberculosis is now generally accepted. Erythema nodosum, on the basis of the experimental evidence cited herein, is in a fair way to be at least partially allied to this group, and it awaits only a sufficient body of clinical evidence and some corroborative work to establish its connection. The fact that the majority of American dermatological texts have not yet given this phase of the matter the attention it deserves, probably accounts for the seeming unfamiliarity of internists, surgeons and general diagnosticians, with the very great diagnostic and prognostic significance of purpura, erythema multiforme, erythema nodosum and the tuberculids. My

own interest in the relation of this group of dermatoses to tuberculosis was aroused by the death of a patient having the miliary type of the disease, following an onset in the form of purpura rheumatica and succeeded by erythema multiforme.

The material here presented forms part of a series of approximately forty cases of erythema nodosum, erythema multiforme with purpura, erythema induratum and the various types of papulo-necrotic tuberculids seen on the service of the Section on Dermatology of the Mayo Clinic during the past two years (1916-1917). The material is presented in a separate communication in the hope of emphasizing the possibility of this form of onset of tuberculosis and of arousing the attention of diagnosticians and internists in this country to its importance from the standpoint of diagnosis and treatment.

The literature on the subject of the association of erythema nodosum with tuberculosis was ably reviewed in 1914 by Foerster, who reported 2 cases of his own. A large proportion of the cases recorded elsewhere were in children. Since Foerster's summary, articles by Nicola (who also cites De Blasi) and Jaquerod have appeared: the former reported 6 and the latter 2 cases. Cecicas considers the good effect of heliotherapy an evidence of the tuberculous origin of the disease. The French investigators, including Chauffard, Sezary, Marfan, Brian and Landouzy, have been especially active in the study of erythema nodosum and have been vigorous proponents of the theory of tuberculous etiology. Landouzy, for example, by his successful inoculation of tuberculosis into guinea-pigs by material from the lesions of erythema nodosum, has supplied the best experimental evidence of the tuberculous nature of certain forms of the disease. Brian has accomplished a similar result. Hildebrandt, in 1907, reported inoculation from the blood at the height of the attack, but interprets his results with reservations.

One of the very interesting features of the etiological developments concerning erythema nodosum is the demonstration by Rosenow in 1915 of a polymorphous gram-negative diphtheroid as the cause of the condition. This organism, whose infection-atrium is apparently the tonsils and pus pockets about the teeth, gives rise especially to the more acute types of the disease. The pathology of erythema nodosum, however, is such that it seems a rash assumption to attribute the changes to a single type of organism. There would appear to be no reason why embolic infarction or thrombosis of terminal vessels in the skin of the extremities, and varying grades of exudation and inflammatory reaction about the affected vessels, could not be produced by living tubercle bacilli in a hypersensitive individual, as suggested by the studies of Rist and Rolland, or by the dead bodies or the "toxins" of the same organism, as suggested by the experiments of Chauffard. While with a larger experience we may

come to recognize clinical differences between erythema nodosum produced by the tubercle bacillus or its products and that produced by the Rosenow diphtheroid, or perhaps by streptococci, the assumption that the pathological differences between the various types will be striking and pathognomonic is in the present uncertain state of knowledge gratuitous. It seems not unlikely that the clinician who ascribes too high a degree of etiological specificity to a condition such as erythema nodosum will fail to recognize many important relations of the picture and will overlook other etiological possibilities which may be of the greatest import to the particular case.

The 10 cases which form the subject of this report in contrast with a number of those reported in the literature occurred in adults. The youngest patient was sixteen years of age, the oldest forty-three; the majority over twenty-five.

CASE 1 (A-202732), a girl, aged twenty-four years, an indoor worker, gave a negative family and personal history. The patient complained chiefly of a cough and an eruption on the legs. For four weeks she had had a slight sore-throat but no tonsillitis. Two days after the onset of the pharyngitis, erythematous nodes, varying from 2.5 to 5 cm. in diameter and from eight to ten in number, appeared over the pretibial region. In color, tenderness, induration and tenseness the lesions were typically those of erythema nodosum; they improved under salicylates and rest. The patient's temperature subsided in two weeks from onset. She had lost 21 pounds in weight during the four weeks of the attack. She coughed, with some expectoration, but a negative sputum examination; no night-sweats or hemoptysis. Examination of the chest indicated signs of a doubtful character over the right lower lobe, with suggestive but not pathognomonic findings in the roentgenogram. The diagnosis was regarded as indeterminate, and the patient was placed at once on antituberculous hygiene. She improved, recovered weight and remained well, although she did not work for six months. In February she had grippe, which lasted more than two months, with loss of strength, weight and appetite. The patient was reexamined in June, nearly a year after the attack of erythema nodosum. At this time breath sounds were prolonged over the right lobe and the whispered sounds were markedly increased. No evidence of active tuberculosis could be recognized in the roentgenogram. She had no temperature, hemoptysis, increased pulse, nervousness or sweats. Antituberculous hygiene was continued, with the patient under observation.

This case from a dermatological point of view was a classical erythema nodosum in every morphological detail. No focus of infection in the form of bad tonsils or infected or abscessed teeth was apparent. The question as to whether or not the patient is tuberculous is, of course, *sub judice*, but should be viewed in the light of the following case.

CASE 2 (A-49238), a male, aged thirty-eight years, has been under observation in the Clinic for seven years. In 1911 he was referred for treatment by his home physician because of shifting pains, stiffness and purpura of ten days' duration. While the patient's physician conceded that the purpura suggested rheumatism, he personally was inclined to suspect tuberculosis of which, in miliary form, the patient's sister had died. Six months before the onset of symptoms the patient had been in bed with "typhoid" for twelve days. At the time of examination purpuric lesions were present on the shins, shoulders and chest. A rise in temperature was reported; he had lost appetite but no weight. Evanescent rales were heard posteriorly over the left lung. Enlarged glands in the left axilla and cervical regions were noted and the roentgenogram showed beginning tuberculosis of both apices; the sputum, however, was negative. In 1914 the patient was again seen for a brief period, but the tuberculous process was then quiescent. In 1918, seven years after the onset of the purpura and three years after the patient was last observed, my assistant was called to see him during an attack of erythema nodosum, which I had the opportunity to observe as it was subsiding. At this time numerous deep subcutaneous erythematous nodes over the tibiae and many less erythematous, smaller and paler shotty indurations, were found. The chain of lymphatics along the left pectoralis major and the axillary and mammary nodes were enlarged and, in some instances, caseous and calcified. Subsequent resection of these glands at operation established the pathological diagnosis of tuberculosis.

This case differed from the conventional picture of erythema nodosum only in the greater pallor and smaller size of many of the nodules, in the absence of the ecchymotic color changes and in the generally lesser activity of the process. At its height, however, it was quite within the usual limits of variation of the clinical picture of erythema nodosum. The purpura, with rheumatoid pains in the early years of the disease observed in this patient, is one of the features common to other cases to be cited hereinafter.

The following case is illustrative of the manner in which a purpuric onset and a tuberculid may precede, by months or years, the gross clinical evidence of active tuberculosis.

CASE 3 (A-154673), a man, aged thirty-one years, a tailor, first came to the Clinic in 1916 because of a scrotal hernia, which was operated on, with good results. At that time the patient gave a history the significance of which was not appreciated until later. A year before his first examination he had an attack of grippe followed by a purpuric eruption. The macules were from a pinhead to a dime in size; some of them had "blistered" and left scars on the extremities. Apart from a small colloid goitre, a hernia and a lichenified scrotum his examination was negative. No radiographic examination was considered necessary in view of the absence of

symptoms. One year and a half after this examination and the operation for hernia the patient returned, giving a history of "sciatica," and of an abscess that had drained through the buttock, and had left a persistent sinus. Bismuth injection demonstrated a draining sacro-iliac abscess. The patient was then seen by a dermatological consultant because of the scars on the legs, which were typically those of a tuberculid, although there were then no active lesions. The operation on the sinus disclosed a tuberculous process, probably originating in the lumbar or sacral spine.

If a dermatologist had seen the purpura and the tuberculid at the first examination two years previously and appreciated its significance a more thorough search might have disclosed the focus.

CASE 4 (A-157847), a woman, aged thirty-three years, a clerical worker, came to the Clinic, in 1916, with a history of severe anemia two years before, from which she had recovered under treatment with iron. A year later a lump, not, however, preceded by any sore-throat, appeared on the right side of the neck. In fact, the patient had never had sore-throat or tonsillitis. Abruptly, two months after coming to the Clinic, and nearly two years after the appearance of the glands, the legs swelled markedly without apparent cause and were covered with raised, red lumps. The patient had a temperature of  $103^{\circ}$  and was confined to bed for two weeks; the temperature subsided but the edema persisted. Examination disclosed a pale, rather fat girl, with numerous erythematous nodules and hyperemic plaques on both legs and arms. The plaques in particular were more suggestive of erythema multiforme than of the conventional erythema nodosum. Their comparative pallor may have been due to the anemia. None of the lesions had shown any tendency to ulceration. The temperature was normal; hemoglobin, 40 per cent.; a marked glandular enlargement on the right side of the neck was shown, by subsequent excision for diagnosis, to be tuberculous. The radiograph of the chest showed healed pulmonary tuberculosis, involving both apices. The tonsils were markedly septic. After the removal of the tuberculous glands a tonsillectomy was performed. This, however, did not prevent the continued appearance of nodular lesions on the legs. Although these did not at any time become ulcerative, the picture approached more and more nearly that of erythema induratum of Bazin, for which we treated the patient a year later.

The typical onset of erythema nodosum in this case, two years after the appearance of the glands, was combined with the appearance of lesions suggestive of erythema multiforme. The nodose lesions persisted and recurred, constituting a chronic erythema nodosum, so to speak, even after tonsillectomy had removed a possible atrium of infection for diphtheroid and other organisms and a block dissection had removed a portion of the tuberculous

focus. There was nothing to suggest a dental source of infection. That the tuberculous focus which was the probable source and perpetuator of the process had not been done away with, is shown by the subsequent re-operation for recurrences in the glands. The following is a case of somewhat similar type:

CASE 5 (A-22802), a girl, aged twenty-three years, a rancher, three years before coming to the Clinic, had sustained surgical removal of cervical glands and tonsillectomy, at which time a pathological diagnosis of tuberculous adenitis was made. The tuberculous process had extended to new glands in spite of tuberculin and an outdoor regime. For two weeks before her examination in the Clinic she had felt tired and her legs had ached, following which an eruption of "lumps" appeared abruptly below the knees on the posterior surface of the legs. These were beginning to involute spontaneously. On examination bluish moderately infiltrated plaques were recognized on the calves of the legs; these disappeared under appropriate treatment. The roentgenogram of the chest was negative. The tuberculous nature of the adenitis had been established by the previous pathological examination and there was a visible and palpable recurrence.

The onset in this case suggests a mild erythema nodosum. In its distribution on the calves and in the relative indolence of the lesions it approached more nearly the type of erythema induratum and should be compared with the preceding case and the last case in the series. The whole picture developed three years after the removal of a tonsillar focus, but while the tuberculous focus was still active. The next case, while perforce left indeterminate, illustrates very well the type of erythema nodosum onset which may eventuate in an active tuberculosis such as that suspected in Case 1 and identified in Case 2.

CASE 6 (A-188556), a man, aged forty-four years, reported at the Clinic with the statement that three weeks before he had caught a common cold. He felt weak since the onset of the infection and had had a cough and expectoration for two weeks. There were some aching and edema of the legs. The past respiratory history was not significant. On examination a very marked right cervical adenopathy was found. The patient's afternoon temperature was 100°. The extensor surfaces of the arms and legs were studded with deep-seated nodules varying from 0.5 to 1.5 cm. in diameter and from a yellowish pink to a deep violaceous color. Over the anterior tibial region there were numerous larger lesions, which were, on the whole, however, somewhat smaller and less ecchymotic than those of a well-developed erythema nodosum, and showed signs of early involution. The lesions about the wrists were of the erythema multiforme type and few in number. A few papulopustules had appeared. Examination of the thorax disclosed prolonged breath sounds and increased fremitus over the right apex. The radio-

graphic examination of the chest, a Wassermann test and the blood culture were all negative.

This case is especially instructive because, in addition to presumptive signs of tuberculosis in the form of localized lymphadenitis, the cutaneous manifestations included erythema multiforme lesions about the wrists, erythema nodosum over the tibiae and a few pustular lesions suggesting the acute generalized miliary tuberculosis of the skin seen in children and more rarely in adults. The lung signs were inconclusive but suggestive.

The next case illustrates how the appearance of an erythema multiforme as a manifestation of obscure tuberculosis may be followed by the development of a tuberculid. The history aligns itself with that of Case 3 (A-154673), who gave a history of a purpura followed by a papulonecrotic tuberculid, as an illustration of the importance of the individual history of cutaneous manifestations in a proper interpretation of the relation of purpura and erythema multiforme to tuberculosis.

CASE 7 (A-224920), a young girl, aged sixteen years, gave an extraordinary family history, on the mother's side, of tuberculosis in both direct and collateral lines. The mother herself had been examined in the Clinic, although not by a dermatologist, and the presence of "yellowish-brown stain-like spots" on the legs had been noted. A diagnosis of anemia and septic teeth was made in the mother's case; the daughter was referred to us on a provisional diagnosis of Raynaud's disease because of the cyanosis of her hands and the history of attacks of "blisters" on the fingers. Her father described to us a fairly typical though abortive attack of erythema multiforme, involving the hands and wrists, which had preceded the present trouble by about four years. The description of the condition at the time of the examination was that of a vernal attack of folliclis, of which the scars were distinctly visible on the dorsal aspects of the terminal phalanges. Similar lesions had developed on the toes. The general examination disclosed the presence of rales and increased dullness over the right lung apex, although the examiner was not in the least under the influence of a preconceived notion about the case, since he had made a diagnosis of Raynaud's disease. Although the roentgenogram of the chest was negative, we advised, in view of the history and the tuberculid scars, that an antituberculous regimen be adopted. The tonsils had been removed for recurrent tonsillitis four years before the onset of the folliclis.

The last case of the series illustrates the association of purpura with a typical tuberculid, erythema induratum and the prominence of arthritic symptoms, which might well lead to misinterpretation of the process in its earlier stages as a septic or rheumatic infection.

CASE 8 (A-233765), a very large, florid woman, aged thirty years, decidedly overweight, whose father had died of empyema and lung

trouble, was referred to my service for a very typical erythema induratum with papulonecrotic lesions and ulceration involving the calves of both legs. On examination it was found that the patient had many cutaneous nodes scattered over both extremities, with purpuric lesions over the arms, trunk and chest. She had an arthralgia and myalgia of the right shoulder which prevented her from raising her arm to her head, and reported that six years before she had had "rheumatic fever." The tuberculid antedated the "rheumatism" by eight years. The teeth were negative, tonsils only slightly septic, roentgenogram of the chest negative and no glands were identified. The tuberculid responded rapidly to treatment, but the nodules in the upper extremities continued to recur.

This case represents a type of patient not unfamiliar to both dermatologist and internist in which a florid and rather obese exterior conceals a focus of tuberculosis which at times cannot be identified. The case is included with the series to illustrate the association of purpura, with a cutaneous lesion whose tuberculous character is now generally conceded.

Before summarizing the lessons to be drawn from such a series of cases I shall further illustrate the diagnostic problems presented by erythema nodosum from the standpoint of tuberculosis by two examples drawn from clinically typical erythema nodosum, diagnosed as such in my records, but with the reservation that observation of their cases shall be continued for some time.

CASE 9 (A-194220), a woman, aged thirty-two years, indoor worker, after being "under the weather" for some time, presented herself looking decidedly ill. She complained of a slight sore-throat, arthritis of the knees and ankles and of having numerous large, deep infiltrated nodose lesions of a dark reddish to purplish color in the pretibial region and on the front of the thighs. Typical lesions of erythema multiforme were found on the backs of the hands and on the neck. There was nothing in the history to lead one to suspect tuberculosis. The tonsils were markedly septic and several alveolar abscesses were demonstrated by the radiogram. The patient showed, however, physical signs of a slight right-sided pleurisy at the base, and the radiogram was suspicious. The erythema nodosum disappeared entirely on salicylates, after which the pyogenic foci were removed and she improved rapidly, all pulmonary signs disappearing to such an extent that a contemplated sanitarium regime was given up.

There are no signs of a tuberculous process in this case four months after the attack of erythema nodosum, but an experience with erythema nodosum of the type illustrated by the foregoing cases would lead one to insist on further observation. Petroff, it will be recalled, has directed attention to the effect of intercurrent infection in temporarily lighting up tuberculous foci to the point at which they can be recognized for a brief time, only to disappear again with the sub-



sidence of the incidental infection. Abt, in 1907, also suggested that it was the function of erythema nodosum to prepare the way for tuberculosis, a conception which loses none of its plausibility in this type of case by the further belief that there may be a true tuberculous erythema nodosum represented by the first eight cases of this series as well.

CASE 10 (A-235299), a housewife, aged twenty-seven years, presented the lesions of erythema nodosum over the front of the thighs and pretibial region, many of them large and tumid, with marked arthritic onset. The patient had lost 15 pounds in weight during eight weeks of the acute process before she was first seen. She exhibited a definite hyperpigmentation overlying a pasty pallor. A history of tonsillitis some years before was obtained. The lesions were not and had not been painful, although in all other particulars they conformed to the strict erythema nodosum type, even to the ecchymotic changes. The tonsils were not septic and the radiogram of the teeth was negative. The patient had a unilateral phlyctenular conjunctivitis, not especially suggestive of tuberculosis. On the other hand, the radiogram of the thorax showed a markedly thickened right hilus, indicating enlarged glands.

Although the patient made an almost miraculous recovery under salicylates it would be folly to release her from further observation for the settlement of the question of concealed tuberculosis. Had her symptoms been accepted at their face value no investigation of this question would have been made and the condition would have been regarded as "rheumatic."

DISCUSSION AND SUMMARY. The series here presented is too small for a satisfactory statistical summary, and for that reason will be incorporated for interpretation in another paper with the group of tuberculids of which it forms a part. Briefly, however, it is of interest to note that the clinical picture of tuberculous purpura, tuberculous erythema multiforme and tuberculous erythema nodosum is made up of objective rather than subjective symptoms. Estimated by a rigorous standard, 4 of the first 8 cases were positively demonstrated as tuberculous, and the remaining 4 were of a highly suspicious nature if not absolutely definite; 2 additional cases of erythema nodosum, morphologically conforming to the conventional or rheumatic type, were also suspected of being tuberculosis and are under observation. Of the 8 original cases the tuberculous focus in 4 was identified by pathological examination; 2 were positive and 1 indeterminate in the roentgenogram of the chest; 4 showed physical signs in the lung and 1 was indeterminate, and 4 had visible and palpable adenopathy. No evidence of syphilis could be identified in any of the 10 cases; 2 of the patients had tuberculids of the papulonecrotic and erythema induratum type, and 1 of them had folliclis, a tuberculid of the fingers; 3 presented purpuric lesions, 3 had lesions of the erythema multiforme type

and 6 had nodular lesions of the type met with in erythema nodosum, though of varying grades of acuteness and severity. In 2 of the cases of nodular erythema the onset was that of erythema nodosum and the localization approached that of erythema induratum. In 1 of these cases the nodose lesions were associated with a typical erythema induratum with ulceration.

Of the 8 cases in the original group 3 presented a family history of tuberculosis and in 1 it was strongly suspected though not absolutely definite. That the onset of the cutaneous manifestations is not necessarily coincident with the onset of the tuberculous infection is apparent from the fact that the shortest probable duration of the active process varied in the cases reported from five months to eight years. The usual points of inquiry in a history of tuberculosis, as to night-sweats, hemoptysis, etc., yielded little information. Two patients only had cough, none had night-sweats and none showed blood in the sputum. The sputum of the 2 who coughed was negative. On the other hand 5 of the 7 of whom data were available showed increased temperatures during the active process, varying from 99° to 103°. Only 1 presented a significant anemia (40 per cent. hemoglobin). The absence of leukocytosis or the presence of a slight leukopenia even in the febrile cases was notable and in keeping with the suspected tuberculous etiology. The counts varied from 5000 to 9600.

The habitus and general condition of the patients afforded little clue to the nature of the disturbance, since the septic cases were indistinguishable from the tuberculous. Loss of weight does not seem to have been a conspicuous feature, although 3 out of the 10 cases discussed showed sharp drops, from 8 to 21 pounds in from five to eight weeks.

The consideration of the possibility of a septic focus in these cases was of interest. In 1 of the patients the tonsils did not seem involved, in 2 they were mildly septic but not markedly affected; a fourth with markedly infected tonsils had them removed without appreciable effect on the process and 2 developed their first attack, 1 of erythema nodosum and the other of folliculitis three and four years after the removal of the tonsils. While gross examination for an alveolar or gingival focus was negative throughout the series of 10 cases, in 1 suspected case the patient had an alveolar abscess demonstrable by the radiogram; 2 cases were negative. Radiograms of the teeth were not taken in the remainder. The secondary focus of pyogenic or diphtheroid infection seems to be a negligible quantity in this group, although its importance is much more apparent in a review of the entire series of tuberculids; 4 in 10 had symptoms of a rheumatic character, in the form of myalgia, arthralgia and neuritis. The modes of onset in the 10 cases were slight sore-throat in 2, cold and grippe in 2, typhoid, so-called, in 1 and by indefinite non-localizing symptoms or the typical abrupt onset of

erythema nodosum in 5. The part played by the respiratory atrium is much more apparent in the larger series.

Dermatologically the differentiation of tuberculous from streptococcal or diphtheroid erythema nodosum can scarcely be worked out on so small a group of cases. A tentative personal view of the matter is as follows: While the two conditions are at times indistinguishable from each other on the score of acuteness, localization and course, and this fact cannot be too forcibly emphasized, the following table embodies the main points of difference as the writer has seen them:

#### STREPTOCOCCAL ERYTHEMA NODOSUM.

Nodes larger, more edematous, and brawny, more tense, and hemorrhagic. May reach the size of a small palm.

Greater involvement of the superficial tissues.

Distribution more apt to be over the front of the lower extremities, especially below the knees and over the front of the thigh; also around the larger joints.

Color changes, more marked than in the tuberculous type. The brown element especially marked. Behaves typically like a bruise.

Symptoms in general more severe, progress more rapid, whole process more acute, tendency to self-limited course.

#### TUBERCULOUS ERYTHEMA NODOSUM.

Nodes smaller, less marked peripheral reaction, hemorrhagic changes less marked. In their place may be purplish lividity, but usually only a well-developed erythema.

Nodules more circumscribed and deeper.

May appear on either front or back of the leg, but tends to localize posteriorly. May appear in smaller numbers or in crops or groups, or one or two on the upper extremities. May appear on the feet.

The nodule is paler at the onset, and progresses from pink to a livid purple or bluish tinge. If it persists (as erythema induratum) it remains bluish, softens and may show a bullous surface or undergo necrotic sloughing. The nodules may present only a mild erythema which subsides, leaving no color changes or only a faint yellow stain, or there may be colorless ones among the erythematous nodes, suggesting Wende's nodular tuberculosis of the hypoderm.

Process more indolent, lesions less tender or even painless, more persistent, may last months or longer, especially if there is little inflammatory reaction. Of material assistance in diagnosis is the concomitant occurrence of an indubitable tuberculid, such as folliculitis, or the papulonecrotic types of lesions or their scars.

Our experience with the diagnostic problems involved in erythema nodosum has led us to formulate for ourselves a series of procedures which should be carried out in all cases in order to establish or eliminate the possibility of a tuberculous infection. First of all, a painstaking search of family and past history for evidence of tuberculosis should be made even though the case seems typically of the rheumatoid type. In the same way the histories of patients suspected of having tuberculosis might well be canvassed for evidences of purpura, erythema multiforme and erythema nodosum. In my experience with the larger group of tuberculids I have been

impressed many times with the fact that a rheumatoid onset in this group of dermatoses should suggest tuberculosis almost as promptly as it does a focus of streptococcal infection. Arthritic and myalgic symptoms seem to have little differential value in eliminating tuberculous infection in these cases. Since the evidences of associated tuberculous infection in this group of conditions are largely objective, painstaking examination of the chest for physical signs, and by roentgenograms should be made in every case. The throat and accessory sinuses should be examined for a collateral focus of pyogenic infection and a radiogram of the teeth should also be a part of the routine examination. Systematic observation of the temperature should be undertaken, with a leukocyte count. A careful search for enlarged glands should be made and repeated. I believe that cases of erythema nodosum are of sufficiently grave prognostic significance to warrant a period of observation and reexamination, prolonged in proportion to the suspicions developed by the study of the case. Finally, I venture to suggest the aid which dermatological consultation can render in such cases. One is surprised to see the readiness with which competent and even highly trained internists dismiss a purpura as "rheumatic," failing entirely to notice the tuberculid, or its scars, which lie beside it, or speculate on the probability of Hodgkin's disease in an adenitis when the evidence to prove it tuberculous is before their eyes in the form of a crop of papulonecrotic lesions. A certain amount of special experience and some special attention to this detail will add much to the diagnostic armamentarium of men in other fields who are called on to diagnose and deal with tuberculosis as a medical and surgical problem.

CONCLUSIONS. 1. While it is impossible at the present time to dogmatize on the existence of a tuberculous type of purpura, erythema multiforme or erythema nodosum, clinical and experimental evidence is collecting to show a close association between a tuberculous infection and cutaneous syndromes of the type mentioned. Whether the lesions themselves are due to the tubercle bacillus, and whether or not their appearance signalizes a flare-up in the tuberculous focus, cannot as yet be definitely stated. It is possible that a non-tuberculous infection which produces the erythema complex may uncover the tuberculous focus, so to speak, much as measles is known to do, and permit a lighting up of a lesion otherwise quiescent. The transition stages apparently existing between erythema nodosum on the one hand and erythema induratum and the tuberculids on the other, together with the experimental evidence cited, would seem to make this view the less probable one. The more probable one, in my opinion, is that which harmonizes with current conceptions of the etiology of tuberculids—that the purpuric, erythematous and nodose lesions are cutaneous reactions to hematogenously distributed tubercle bacilli, deposited in a hypersensitive

skin and originating in a tuberculous focus sometimes unrecognized perhaps for many years. Whether the tuberculous phase is the cause or the consequence, the frequent clinical association of the cutaneous symptoms with this disease loses none of its importance from the standpoint of diagnosis and therapy.

2. Since the clinical appearance of the eruptions discussed does not in my opinion offer adequate means of differentiating "tuberculous" from non-tuberculous forms, every case of purpura, and many cases of erythema multiforme, should, I believe, be subjected to a preliminary survey for the possibility of tuberculous infection. Every case of erythema nodosum should be subjected to an even more searching examination.

3. The search for a focus of tuberculosis should employ the usual evidence elicited from the history, weight and temperature curves and radiograms and physical examination for pulmonary and glandular signs (present in 8 out of 10 of the cases) here presented. The teeth and the nose and throat should be systematically examined for collateral foci of pyogenic infection, and dermatological consultation sought for seemingly trivial lesions on the fingers, face and legs, for scars and pustular lesions on the trunk, macular pigmentation, etc., to say nothing of the more obvious cutaneous signs of tuberculosis, such as erythema induratum, papulonecrotic tuberculids and folliculitis (present in 3 of our cases).

4. Cases of erythema nodosum, whatever their type, should be subjected to periodic reexamination and observation.

5. In the absence of a demonstrable source of pyogenic infection, and even in its presence, the possibility of tuberculous etiology should be seriously entertained and an antituberculosis hygiene considered.

6. The results of the application of the foregoing principles and routine to the dermatoses mentioned, while only partial as yet, have shown so high a percentage of demonstrable and suspected tuberculosis, pulmonary and glandular, osseous and cutaneous, as to lead the writer to suspect that the association is more than coincidental and that it can safely be made a basis for diagnostic and therapeutic decisions in a considerable percentage of cases.

7. It seems not improbable that erythema nodosum especially may be a syndrome of tuberculous as well as diphtheroid or streptococcal origin in an as yet unestablished percentage of cases.

8. Erythema induratum would seem to be susceptible of interpretation as, in a sense, a chronic ulcerative phase of tuberculous erythema nodosum, since intermediate types appear in this series.

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**ACUTE PULMONARY EMPHYSEMA OBSERVED DURING THE  
EPIDEMIC OF INFLUENZAL PNEUMONIA AT CAMP  
HANCOCK, GEORGIA.**

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PRIOR to the epidemic of influenza at Camp Hancock there occurred in one company an outbreak of hemolytic streptococcus infection of peculiar virulence and uniform course. There was reason for thinking that the spread of disease in these cases was by food or milk infection. One man primarily developed this trouble and in a few days six other men were affected simultaneously, all showing

aphonia, paresis of the soft palate, inability to swallow on account of choking, substernal pain, but otherwise no other subjective symptoms except cough. The expectoration became more profuse, bronchitis developed and three of the seven patients died. The temperature and pulse in all of these patients was practically normal throughout the course of their illness. Dyspnea developed as bronchitis increased, and it seemed to us that these patients really were drowned by the thick pus which they were unable to expel from the bronchi and trachea. Autopsy in these cases showed a streptococcus infection, with a remarkable affinity for the trachea, and gradually extending down through the bronchi. There was visible peribronchitis and peritracheitis. The larynx and the lungs escaped invasion. This series of cases is mentioned because there were many points of similarity with the bronchitis which accompanied influenzal infection later, and which showed uniformly a bronchitis and peribronchitis very similar to these cases but accompanied by pulmonary emphysema and so-called bronchopneumonia.

During the latter part of September there appeared at the camp an outbreak of disease which did not resemble influenza clinically, but which increased rapidly in frequency until during the last week of that month there were admitted to the hospital about 450 patients with this acute infection of the upper respiratory tract. These showed a mild coryza and conjunctivitis, some pharyngitis, very little bronchitis, frequently mild acute sinus symptoms and some slight cough, mild fever, brief course, and no severe pains. A number of cases of pneumonia developed among the patients. We had, during the epidemic, three wards of these so-called "Camp Hancock" pneumonias which were typical lobar pneumonia clinically. They all showed prune-juice or rusty sputum, high temperature, as a rule, with rapid course and termination by crisis. They all showed typical signs of consolidation in some portions of the lung. In many cases the course was brief after admission to the hospital, and, in fact, some of them seemed to be admitted just prior to crisis. We were able to keep those patients isolated from the bronchitis cases during the epidemic, and while the epidemic bronchitis wards were showing a mortality of nearly 40 per cent., there were only a few deaths among these pneumonia patients (under 5 per cent.) These acute upper respiratory infections, while not considered influenza at that time, appeared to exert a protecting influence when the real influenza appeared, and we were forced to the conclusion that an attenuated influenzal infection must have been responsible for the mild epidemic.

About October 1 there arrived at the camp over 2000 men who had become infected at another camp and had then been subjected to a prolonged railroad journey. The crossing of infections during this long journey produced a profound infection similar in all the patients and presented a very clear-cut clinical picture in this large group of

men. We admitted to the hospital in all about 1800 of these cases. They were characterized by:

1. Prostration—incident to the disease and added to by the fatigue, hunger and lack of care unavoidable during the long journey.

2. Cyanosis—particularly of the face and ears and intensely red conjunctivæ and dusky red pharynx.

3. Dyspnea—some degree of dyspnea was invariable; breathing was very shallow.

4. Epistaxis—very frequent, probably in nearly half the cases, and in many instances severe in degree.

5. Bloody sputum.

6. Cough—all had cough and showed signs of bronchitis in varying degrees of severity.

7. Extreme lethargy—a typhoid state, clear sensorium, but apathy and drowsiness; very few were delirious.

The patients suffering from influenza who recovered without marked pulmonary complications were, as a rule, convalescent within a few days and did not experience the nervous or renal complications which have been reported as so frequent in previous epidemics. Many of these men developed their bronchitic emphysema during the first day or two of influenza, others were apparently convalescent from the influenza and seemed ready for discharge to duty when there was a sudden onset of the so-called pneumonia, with characteristic change in the physical findings.

In the so-called pneumonic cases there was evident absent breathing, with impaired resonance at the bases and hyperresonance over the rest of the chest. We were struck with the burly appearance of these patients. This appearance was due to the distention of the neck vessels and erection of the chest, which was dilated to the full inspiratory limit. These patients showed increased temperature, with bloody sputa, and large areas of absent breath-sounds, diminished vocal fremitus, and above these areas crepitant rales in circumscribed zones and diffuse bronchitis throughout the lungs. Forced breathing might bring out rales where sounds had been absent. If breath-sounds reappeared the expiration was markedly prolonged. In no case was the sputum of the rusty or prune-juice type, but was foamy and bloody, and sometimes mixed so completely as to resemble tomato purée. Areas of dulness appeared in the bases, gradually spreading from below upward, and the sputum became frankly purulent or remained bloody, but was not viscid, as in pneumonia.

The temperature was irregular, always elevated but not unduly high; these patients might have sweating throughout the entire course of the disease. The pulse was slow for the temperature, suggesting reflex vagus inhibition from pulmonary distention. There was no arrhythmia and the heart remained apparently good



to the end. With the finding of dulness in the bases, which might occur within a few hours of the appearance of the areas of absent breathing, patches of tubular breathing would appear as in bronchopneumonia. These small areas of dulness rapidly coalesced until the whole base of the lung showed signs as in a lobar pneumonia, with marked percussion changes, sometimes flatness, and tubular breathing with egophony and whispered pectoriloquy, as in lobar pneumonia, often without rales.

The rapid massive involvement was accompanied or even preceded by the generalized pulmonary emphysema. Whether this was due to inflammation of the lung parenchyma, causing a loss of tone, or to nervous or circulatory trophic changes, causing loss of tonicity, or to bronchial blockage with valve action production is not clear and will not be discussed here. The sudden occurrence of profound emphysema in these cases as the outstanding feature of the condition was unmistakable. At this stage of consolidation, as at the prior stage of absent breathing, there was evident above the thus affected area a portion of the lung which was apparently compressed and showed diminished or absent breathing, impaired percussion note, and on forced breathing, or after hard coughing, showers of fine crepitant rales as the compressed lung unfolded. We consider this sign of changing areas of compressed lung a fairly constant sign of emphysema. The total lung volume is too great for the chest capacity, and some portion of the lung is usually compressed with other portions fully distended, these areas changing after deep breathing or coughing, with breath-sounds and percussion resonance being reestablished in the expanding portions.

The areas of consolidation appeared usually posteriorly almost always on one side, followed by the other, spreading and coalescing toward the lower limits of the lung until the base was universally involved, then gradually spreading upward, one side more than the other, but seldom with one side wholly free from involvement. The total consolidation appeared as a gradual filling from below up. Bronchitis persisted throughout, but tubular breathing and pectoriloquy became pure in the solid portion, reaching perfection at the lower levels. Subcrepitant rales were typical in some portions.

The point that struck us here with great force was the intense dyspnea, with little cardiac disturbance, cyanosis, great air hunger, and erection of the chest fixed in a state of hyperinspiration, with only tidal air movement. As the muscles of respiration failed exitus occurred, a respiratory death, in contradistinction to the toxic circulatory or vasomotor death commonly seen in the early days of true pneumonia. The pulse impressed us as being slowed as if under the influence of cardiac vagotonic inhibition, as in high pulmonary pressure. The pulse in desperately ill or moribund individuals was excellent in volume and quality, and relatively slow; arrhythmias were almost never noted. As this distention of the chest developed

it could be noted that the whole chest excursion was diminishing as manifested by a general diminution of the lateral excursion of the costal arches until there was an inspiratory retraction, more in the affected side at the onset, then becoming bilateral.

Very soon the accessory muscles of respiration were the only effective ones giving a lift of the upper chest, while over the rest of the thorax was seen only a weak effort of the muscles, giving an undulatory movement of the chest, already so overdistended that any gain in capacity was impossible. Sternal tympany became more marked, assuming a box-like character. Marked stasis of all the veins entering the chest and those drained by the superior vena cava were manifest. Cyanosis became more profound and in the end stage there was an ashen lividity of the whole face and chest.

When in apparent respiratory extremis, frequently a patient would begin to complain of pains, substernal and in the jugular fossæ, and crepitation would be noted in the subcutaneous tissue at the root of the neck, and immediate marked subjective relief was apparent, rapidly followed by a noticeable improvement in the respiratory excursion of the chest, and the most striking decrease in cyanosis and jugular distention. With the relief of cerebral venous stasis a clearing up of the previous accumulative mental hebetude occurred with remarkable suddenness. Cutaneous emphysema soon became diffuse, not infrequently spreading down the trunk to the pubes, first appearing along the sheaths of the cutaneous veins. As the intrathoracic pressure was thus relieved these apparently moribund patients often went on to recovery. We then began measuring the respiratory excursion, the measurements being taken by Lieutenant Beveridge, and his measurements verified these clinical observations, in that there was apparent an increase in the chest circumference during the illness and an abnormally small respiratory excursion, with a striking increase immediately as the cutaneous emphysema gave vent to the air contained in the mediastinum.

The emphysema of the lungs and mediastinum was shown by the marked sternal and vertebral tympany, the disappearance of cardiac dulness and the low stand of the diaphragm, with the pleural sulci distended in full, marked limitation in the motion of the ribs, inspiratory retraction of the costal arches and marked cyanosis. The extent of the emphysema was so great that the supraclavicular and suprasternal fossæ were obliterated and the upper interspaces bulged on expiration and markedly on coughing. It was difficult to outline consolidations in the bases, because the percussion note over the whole chest was so hyperresonant and also because the lung tissue was found to be air-containing.

The course of the disease was entirely different from that of lobar pneumonia. This contrast was particularly striking, as we had at this time three wards of pneumonia patients, all of whom showed typical prune-juice sputa and termination of acute, severe, fre-

quently toxic courses by typical crisis. These cases, which were kept carefully isolated from newcomers, recovered without marked bronchitis and furnished an opportune contrast for comparative observation. We could not fail to be impressed by the presence in one group and the absence in the other of the characteristics noted above: namely, the peculiar type of sputum, cyanosis, dyspnea, respiratory movements and extreme emphysematous fixation of the chest, almost as in an animal in anaphylactic shock. Most of about 1800 patients received after a long railroad journey, with a profound degree of infection and thorough crossing of all the infectious strains, showed some degree of bronchitic emphysema and gave us an unusual opportunity for observing a condition developed to its greatest degree of uniformity and intensity.

The sequence in these cases is usually as follows: At the onset signs of generalized bronchitis and emphysema, universal throughout the lungs and most marked at the bases and toward the roots of the lungs. This is the stage of absent breath-sounds in the area which is about to show signs of consolidation.

Roentgen-ray plates taken at this stage are peculiar in that while the percussion note is resonant or hyperresonant throughout the chest, and the breath-sounds are diminished in intensity and not roughened, the skiagraph shows a diffuse clouding of the whole lung, with the bronchi clearly outlined, broad and dense, giving a streaked appearance, as in a moderate degree of bilateral fibroid phthisis.

The next stage showed continued universal bronchitis, with patches toward the bases showing the auscultatory signs of consolidation, which rapidly coalesced until these areas became diffuse, rapidly advancing upward, always bilateral, though the involvement in one side might be limited in extent. These signs were particularly well-marked in the back. The percussion note was altered by the emphysematous condition of the lung, so that a true flat note as elicited in pneumonic consolidations was not found. A note might sound almost flat in comparison with the hyperresonant or tympanitic note found in other portions of the chest, but careful analysis always has shown that there was a large factor of resonance or high-pitched tympany when this area was considered by itself. It may be noted here that these apparently solid lung portions all were air-containing and floated high in water. This is the stage in which the tympanitic note on the sternum becomes so marked, cyanosis and dyspnea extreme, the chest erected to its greatest capacity as if filled with a lung which is too large for the thoracic cage and the respiratory excursion practically obliterated. Toxic signs were not evident and pulse and temperature relatively low as compared with pneumonia. Delirium was comparatively infrequent and the anxiety and mental distress so marked in pneumonia were strikingly absent.

A number of the patients dying in this stage of early emphysema

came to autopsy. The cause of death was evidently the mechanical obstruction of the return flow of the venous blood from the general circulation to the interior of the chest by the thoracic fixation interfering with the mass movement of the blood. Dilatation of the right heart cannot be demonstrated clinically in these cases possibly because of the overlying emphysematous lung and tympanitic sternum, and probably because these hearts are not dilated as in pneumonia and certainly not sufficiently dilated to account for the enormous distention of the superior and inferior vena cava as a prime factor in this stasis. This stasis in the large veins appeared to be due to the obstruction occasioned by increased intrathoracic

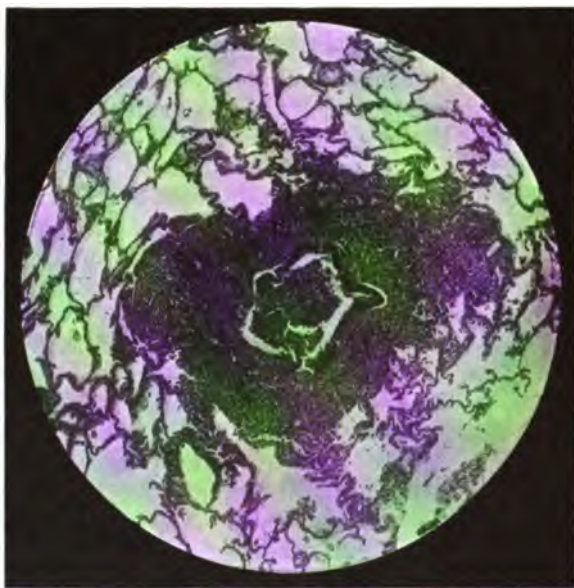


FIG. 1.—Bronchitis, peribronchial infiltration and acute emphysema, with turgescence and infiltration of the alveolar walls.

pressure, and the relief of stasis following immediately upon the escape of air from the mediastinum into the loose areolar tissue surrounding the large veins was one of the most striking features of the whole series of observations and was comparable to the relief afforded by venesection in the distress of acute cardiac dilatation.

While we had many autopsies showing this stage of the disease, one of the most graphic demonstrations of the extent of this emphysematous dilatation was afforded by the necropsy finding in the case of patient "G." In this case true lobar pneumonia supervened as a reinfection on an existing bronchitic emphysema and involved the upper and middle lobes on the right, making a perfect cast, measuring 40 cm., on the convex surface, 24 cm. on the concave and

15 cm. at the hilus. The rib markings deeply indented the surface. This cast by preventing any collapse of the lung showed the enormous distention which these lungs can attain.

The lungs of bronchitic emphysema at this stage showed a great similarity in gross pathology as well as in clinical findings. The lungs were gray toward the apex, with a uniform beefy red appearance toward the base. The surface was glistening, showed the rib markings and emphysematous bullæ, which were plainly visible under the visceral pleura. The emphysema was such that the lungs could not be collapsed by pressure, and while fairly tough at the apex were extremely friable at the bases. Here the tissue, while appar-

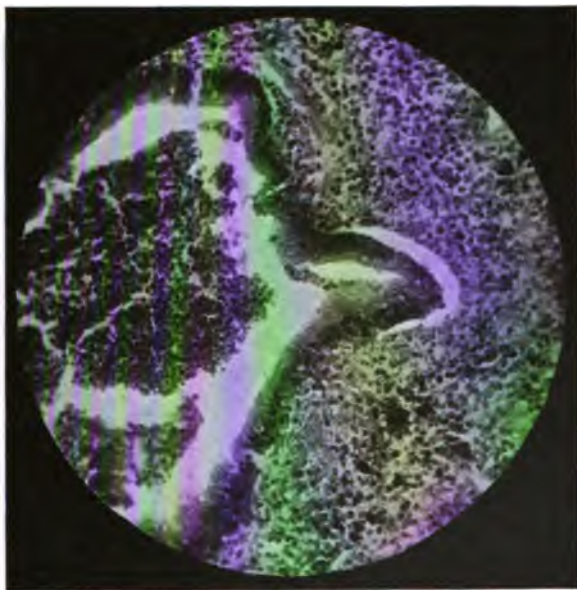


FIG. 2.—Portion of section shown in Fig. 1 under high power, showing changes in the columnar cells lining the bronchus, and the surrounding round-cell infiltration.

ently solid, was always found to be air-containing, floated in water, and although elastic to a light touch, disintegrated under moderate pressure, appearing almost necrotic.

The cut surface showed color as on the pleural surface, and from the red portions bloody serum exuded. The surface was glistening and pulled away from the bronchial stumps, which stood out prominently, showing thickened indurated walls and infiltrations surrounding them in cross and longitudinal sections and exuded thick, creamy pus. This poured out in quantity from the large bronchi. All lobes of the lung were studded with nodules from the size of a millet-seed to the size of a bean, which were inflammatory areas surrounding sections of the bronchi and bronchioles. Thick aggregations of

these formed irregular nodules, which simulated lobular consolidations; but to the touch these lungs had a feeling which was similar in all of them and quite characteristic. While the nodules varied in number and degree of coalescence they were distinct from lobular pneumonia, and of all pathological lung processes with which we are familiar they resembled only acute disseminated pulmonary tuberculosis. In looking at these lungs it seemed impossible that such lungs could clear up without multiple abscess formation or extensive necrosis. The lung parenchyma in the bases between these inflammatory nodules was mushy and friable. It seemed as though the blood supply and innervation must have been interfered with by the peribronchial infiltrations. The hard nodules were lacking in

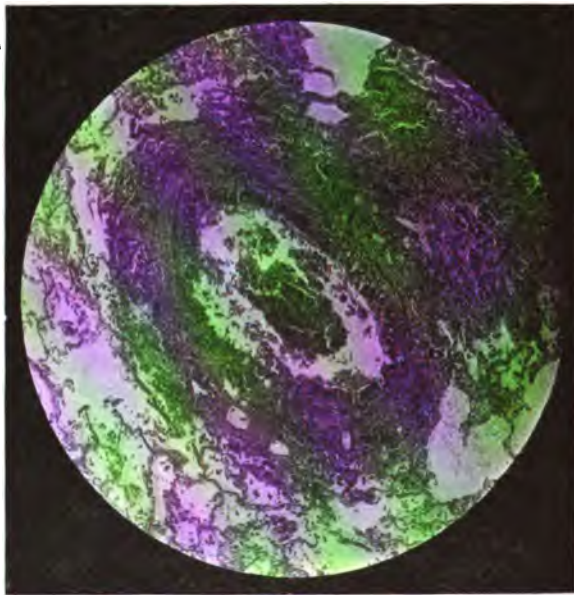


FIG. 3.—Coalescence of peribronchial infiltrations in the evolution of consolidations.

those cases in which death occurred in the first days of the disease, but the same necrotic character of the lung parenchyma was present and the thickening of the bronchi evident. Pleural involvement was practically absent and empyema not found.

When convalescence was prompt and large abscesses or pleural fluids did not develop, the patients apparently recovered remarkably quickly and did not appear like men who had been through a course of pneumonia. The toxic depression was lacking and they looked remarkably well, but rales persisted throughout the chest and peribronchial fibrosis was marked. From the roentgen-ray plates one would say that there was present much lung destruction and permanent damage.

Other patients who were slow in convalescing showed an irregular temperature curve with febrile exacerbations, continued generalized bronchitis and purulent expectoration. The peribronchial thickenings and infiltrated areas, standing out clearly and separated by emphysematous lung, were so generally distributed and so close together in the roentgen-ray plates of these chests that the descriptive term "snow-storm" was applied to these plates. Multiple small abscesses were always present, thickly strewn throughout the lung, and these patients might die without the development of large areas of necrosis with empyema which frequently terminated the struggle for life.



FIG. 4.—Photograph of thoracic contents removed entire, showing large emphysematous bullae of lung and particularly of mediastinal alveolar tissue. Specimen preserved in Kaiserling's fluid.

We encountered nothing resembling the primary empyema or extensive early pleural involvement accompanying the active pneumonia observed in the epidemics of bronchopneumonia of a year ago. When fluid was found in our cases it occurred late and seemed always due to a direct extension to the visceral pleura from an underlying inflammatory focus. The fluid always occurred late and if explored when first appearing was usually clear straw colored and coagulated promptly on withdrawal. If such a fluid was withdrawn by aspiration almost invariably sticky frictions were audible within a few hours. If reaccumulation of fluid occurred it was, as a



rule, distinctly purulent or sometimes fibrinous, making aspiration difficult.

Collections of fluid were in thin layers as if they had accumulated in the pleural cavities under pressure of the emphysematous lungs, which afforded insufficient space for the usual localization in the dependent portions of the chest and forced the fluid along the paths of least resistance, frequently upward and along the anterior mediastinum.

There was dulled tympany corresponding to the fluid, but percussion alone gave little distinction between areas of consolidation and fluid. These thin layers of fluid under high tension apparently served as excellent transmitters or conductors of voice and breath-sounds as well as of tympany to percussion from the compressed emphysematous lung beneath them. They did, however, act as mufflers in diminishing the amplitude of the vibratory waves, and we found that pure high-pitched tubular breathing, whispered pectoriloquy and egophony were the most reliable signs of fluid even though tympany was marked over these areas of effusion.

When the chest space was reduced by rapid collection of fluid in the pleural cavity, the emphysematous upper portions of the lung were pressed against the walls of the upper chest. These lungs (as noted invariably at autopsy) could not be collapsed by pressure, and the resulting signs were very different from those found where a normal or non-emphysematous lung is compressed by a large pleural effusion. We noted in these cases signs practically indistinguishable from those found in large cavities or open pneumothorax. The apices gave a perfect tympany to percussion and cracked-pot sound and a ringing character of the spoken voice, with amphoric transmission of tracheal breath-sounds. These localized fluid collections, rapidly walled off and under pressure, were frequently accompanied by severe diffuse pain in the axillary region of the affected side, with skin hyperesthesia and tenderness in the interspaces. It was noted that in the 6th, 7th, 8th, and 9th spaces, particularly the latter, the pain was constant even in the absence of respiratory motion, but accentuated on deep breathing or coughing.

The fluids varied in their bacteriological flora and in their physical characteristics. They were uniform in their late occurrence, sometimes six weeks from the onset of the bronchitis, from the fact that they were not the result of a diffuse pleuritis but started as exudates from relatively small areas of pleura overlying the inflamed or necrotic lung tissue. There was uniformity in the rapidity of formation of adhesions; indeed, so far as we could judge from physical signs and from autopsy findings the fluid was often found after adhesions had established themselves and started as softening in a mass of plastic exudate. Massive empyema was hardly ever encountered. A number of cases at autopsy showed the lung tissue at the bases so necrotic that we looked carefully in other patients for signs of lung



rupture and consequent empyema. This did not occur early, but eventually a number of patients showed rupture of lung abscesses into the pleural cavity. This rupture occurred after adhesions had formed and the empyemata thus developed were strictly localized and in some cases the bronchial drainage was sufficient to clear them up, at least temporarily. These patients with ruptured lung abscess frequently succumbed after a more or less prolonged septic course. The auscultatory signs of these conditions were well-marked and resembled those of large tuberculous cavitations, with whispered pectoriloquy and bubbling rales very close to the ear. The destruction of lung tissue by necrosis and abscess formation in these cases, as shown at autopsy, was enormous, almost total in the bases; usually parts of the upper lobes were also destroyed, the remaining lung tissue being markedly emphysematous.

Regarding treatment it must be said that no routine treatment was shown to be of value after the bronchitic emphysema was established. In view of the apparent immunity enjoyed by individuals who had recently suffered from attacks of probable influenza of a mild form it would seem that a proper vaccine might be of prophylactic value when influenza is epidemic. Creosote in full dosage in the influenza cases may be of service in preventing the development of bronchitis.

When bronchopneumonia with bronchitis and emphysema is established the therapeutic measures which are useful in the management of lobar pneumonia are of no avail. The emergency is due to mechanical rather than toxic causes, and the problems presented are totally different.

**SUMMARY.** Observation of 1150 soldiers with epidemic influenza pneumonia at Camp Hancock has indicated that the disease as it occurred there differed so essentially in its pathology and course from lobar, broncho- or lobular pneumonia, according to the usual conception of these diseases, that we designated the condition as Acute Bronchitic Emphysema.

Certain conditions were invariably present, including an intense bronchitis and peribronchitis similar to that found in a previous epidemic of pure hemolytic streptococcus infection. There was also present from the first a destructive softening of the lung parenchyma. In addition to this there was always an early and persisting generalized pulmonary emphysema which frequently was the main factor in causing death by interference with the mass movement of the venous blood. These conditions were found in every case examined at autopsy. Except for frequent acute otitis media there were almost no complications or sequelæ outside of the chest.

The pulmonary emphysema, with consequent venous stasis, accounted for the cyanosis, epistaxis and fixation of the chest in the phase of extreme inspiration, with low stand of the diaphragm, which characterized these cases, and also accounted for the paradoxical physical signs in cases in which fluid developed in the chest.

**PRIMARY CARCINOMA OF THE THIRD PORTION OF THE DUODENUM.<sup>1</sup>**

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PRIMARY carcinoma of the duodenum is a rare disease. Only 7 cases are reported by Schleringer in 42,000 autopsies made in Vienna. Perry and Shaw in studying the Guy's Hospital Reports found only four examples in 18,000 autopsies. Out of 19,500 autopsies done at the London Hospital 18 cases were found.

Carcinoma of the duodenum comprises about 2 per cent. of the cases of primary malignant disease of the intestine. The disease may occur in any part of the duodenum. Of Fenwick's 57 collected cases the first part of the duodenum was involved in 21.5 per cent., the second part in 57 per cent., and the third in 13.5 per cent.

The majority of these tumors belong to the cylinder-celled type, but colloid cancer and spheroidal-celled types occur. Adenocarcinoma usually encircles the gut and causes a constriction of its lumen, while the spheroidal-celled carcinomata either take the form of soft excrescences or of deep ulcers, with elongated edges and fungated bases.

This case was an adenocarcinoma, involving the third portion of the duodenum below the biliary papilla. It encircled the bowel wall and produced almost complete occlusion. It was primary and no other organ was involved. Before proceeding to give the history of the case, I wish to review the symptomatology of the disease. The clinical picture presented depends upon the location of the growth in the duodenum. Carcinoma above the biliary papilla—namely, in the horizontal portion of the duodenum—presents the symptoms of pyloric stenosis, beginning with discomfort and flatulence after meals, with later pyrosis, loss of flesh, anemia and finally vomiting of a persistent type, with or without hematemesis. A palpable mass is usually present. Carcinoma in the vicinity of the biliary papilla—namely, in the second part—is ushered in with a slow developing icterus without pain or vomiting. Chills and fever may be present. The jaundice persists, vomiting develops, the liver becomes enlarged, the gall-bladder may be distended and palpable, there is progressive loss in weight and strength and the patient dies in inanition. A palpable mass may or may not be present.

In carcinoma of the third portion of the duodenum the first symptoms, according to Fenwick, consist of flatulence and discomfort after meals, burning acid eructations, loss of appetite and gradual emaciation. After a lapse of a few months vomiting appears and

<sup>1</sup> Presented before the Minnesota Pathological Society.

persists until the end. (In this case the vomiting was intermittent and there were months in which the patient was free from it.) The tongue becomes thickly coated and thirst becomes excessive. (In this case the tongue was clean.) There is marked cachexia and rapid loss in flesh. (In this case no real cachexia and no persistent loss in weight until near the close, but, on the contrary, a gain of eight to ten pounds during one interval of the illness.) The bowels are obstinately constipated. (In my case the bowels could always be moved by a saline.) The stools are seldom quite devoid of bile and often contain altered blood.

The character of the vomiting is an important feature. It always contains bile, which gives it a bright green color. The filtered vomited material is neutral or alkaline in reaction. (In this case it was acid.) It contains no free hydrochloric acid, but usually lactic acid. (The contents always contained free hydrochloric acid in the case reported and contained no lactic acid.) Will digest fibrin if warmed, owing to the fact that it contains pancreatic juice. (This test was not made in my case.) From time to time attacks of intestinal obstruction intervene, attended by incessant vomiting and obstinate constipation. At these times from 10 to 15 pints of an alkaline bilious fluid may be vomited in the twenty-four hours, notwithstanding the fact that the patient has taken nothing by mouth.

Examination of the abdomen shows a much enlarged stomach, with pronounced succussion as far out as the right mammary line. No tumor, as a rule, can be palpated unless the retroperitoneal glands are involved, when an ill-defined hard mass can be felt to the right of the umbilicus. The introduction of a stomach tube gives evidence of considerable importance. After the stomach has apparently been emptied a fresh gush of fluid gastric contents appears, with cough, or when the body is bent to the left, due to the regurgitation of the duodenal contents. After the stomach has been evacuated a succussion splash may be obtained to the right of the navel, owing to the presence of fluid in the duodenum. Finally, after emptying the stomach at night, a quantity of bilious fluid may be again extracted in the morning before food is taken.

**CASE HISTORY.** Mr. G. H., aged seventy-four years, married, children, a man of large affairs. No cancer history in his parents. Had been strong and well as a young man. For the past seven or eight years had had distress in his upper abdomen and back from time to time. He was a very heavy eater, and these spells were attributed to indiscretions in his diet. The distress was never acute, but he would complain of some ill-defined soreness in the upper abdomen. He would often vomit once or twice. The spells never continued for more than a few days, and would then disappear. During the later years of his life he had been subject to attacks of bronchitis in the winter. In some of these his breathing had bothered

him, especially at night, and in one or two he had had some cardiac disturbance, with a weak, feeble, rapid pulse. Had had casts and a little albumin in his urine for years. Had taken a moderate amount of stimulants all his life.

In the latter part of November, 1916, following the death of his wife, it was noticed that he seemed pale in color and lacked his usual vigor and energy. No thorough examination was made at the time, as his attending physician attributed the state of health to the trying circumstances surrounding the death of his wife. He was sent to southern California for the winter. While going over the mountains the nurse noticed that he complained of distress in his chest and became pale and weak. After reaching Santiago he was thoroughly examined by an internist and a diagnosis of pernicious anemia was made. No nucleated reds were, however, found in his blood. The blood examination at that time showed 2,500,000 reds and 55 per cent. to 60 per cent. hemoglobin. He had some gastric symptoms in January, 1917, and one or two vomiting spells. In February he had more gastric distress, with vomiting lasting over a month's time. From this he recovered and felt splendidly for about a month, when he again had an attack of persistent vomiting lasting three or four days. He retained nothing upon his stomach during this attack, and the vomited material was dark brown in color. In this attack he vomited large quantities of fluid—in fact, more than he took in. He returned to Minneapolis in May, much improved, and the blood examination, made by his physician, showed 4,000,000 reds and hemoglobin 56 per cent.

I saw him first in June, 1917. He was in one of his vomiting attacks. Had been vomiting two days or so. Was getting up large quantities of dark and greenish-looking fluid, with many black, partially digested blood-clots in it. The fluid vomited was much more than he was ingesting. Would vomit a bowlful at a time. The appearance of the vomited material suggested cancer of the stomach, and this diagnosis had been considered on account of the man's age; but the absence of a palpable mass, the fact that he had maintained his weight, his perfect relief from gastric symptoms between attacks, his high-grade anemia and the negative roentgen-ray examination of the stomach for carcinoma had been considered sufficient evidence for ruling this out.

The physical examination revealed a large-framed, well-nourished man, with iron gray hair. The color of his skin and mucous membranes showed marked anemia, not the typical waxy color of pernicious anemia. He was weak from the vomiting, but had been up and about at home prior to this attack, and felt good. He complained of no numbness of the hands or feet. Nothing of importance was noted outside of his color, a systolic bruit at the apex of the heart, without cardiac enlargement, and a somewhat emphysematous chest with quiet breath-sounds. No enlarged glands or hard nodules in the

skin could be felt. A small lipoma, the size of a bean, was present in the abdominal wall of the upper right abdomen. This at first was confusing and was interpreted as intra-abdominal. No mass could be palpated in the abdomen. The rectal examination was negative. Distention of the stomach with gas showed a large stomach, the greater curvature being below the umbilicus. No mass could be palpated after gas distention. No peristaltic waves could be seen sweeping over the stomach. Marked succussion was present over the stomach area. The liver was not enlarged. The spleen not palpable. No masses could be palpated in other parts of the abdomen.

The examination of the vomited material showed a strongly acid reaction; free hydrochloric acid 6, total acidity 20; no lactic acid; strongly positive benzedine; no Oppler-Boas bacilli. The gastric analysis following an Ewald meal showed free hydrochloric acid 59; total acidity 100; no lactic acid; negative benzedine.

The blood examination showed hemoglobin 45 per cent.; reds, 3,900,000; leukocytes, 7000. Differential count: polynuclears, 71 per cent.; large mononuclears, 2 per cent.; small mononuclears, 23 per cent.; transitionals, 2 per cent.; basophiles, 2 per cent.; no myelocytes; no nucleated reds.

The urine was acid; specific gravity, 1018; contained some albumin; no sugar; an occasional pus cell; a few small, narrow hyaline and granular casts. The stools showed a strong benzedine test for blood.

We had then here to deal with an old man, well-nourished, looking very anemic, complaining of ill-defined gastric symptoms, exhibiting at times periodical attacks of vomiting of large quantities of greenish material, with partially digested blood, whose physical examination revealed a high-grade secondary anemia, without assignable cause except the presence of blood in the vomit and in the stools. Roentgenoscopic examination of the stomach and bowel was refused on account of a former unhappy experience when previous roentgen-ray examinations had been made.

The primary examination was made June 23, 1917. The patient was observed closely from that time until his death in coma, about seven months later, and one year and two months subsequent to the time when he first presented symptoms of anemia. I wish to give you as nearly as possible an outline of the clinical course, with the blood, gastric and stool studies during this period.

The note of June 27 read: I saw this patient at his house last night. Was feeling much better, retaining all his food. Says he does much better on a solid than on a liquid diet. Is now eating toast, soft eggs, breakfast foods, etc. I palpated the upper abdomen. Could feel the little-finger-sized nodule to the right of the median line, close to the right costal margin. It is probably in the abdominal wall. It is tender to touch and not very hard. Could feel no enlarged

glands. No evidence of metastatic nodules or anything suggestive of malignant disease.

Note of July 7 read: Examined Mr. G. H. today. Patient is getting on very well on his diet of rice, milk toast and cereals. He has not vomited. He is not losing weight and feels good. In the mid-abdomen, about midway between the tip of the ensiform and the umbilicus, I could feel a deep-lying resistance, which I could not outline. This spot is tender to touch on firm pressure. Examination of the stools shows occult blood. Have placed the patient on treatment for duodenal ulcer.

July 16. Examined patient again today. Says he is comfortable, more so than he has been for a long time. Has had no vomiting. Could palpate no mass or tenderness in the abdomen. Is eating only rice and bread and milk. Is fed every two hours. Is gaining in weight. Occult blood is still present in the stools, but the reaction is not as pronounced as before. Blood examination shows hemoglobin, 64 per cent.; red cells, 3,732,000.

August 28. Patient feels much better. Is almost free from abdominal distress. No vomiting. Sleeps well. Still on soft diet. Is gaining in weight. Stools show occult blood. Can palpate no mass. Hemoglobin, 58 per cent.; reds, 3,253,000.

October 1. Patient looks a trifle paler. Up and about each day. Is complaining of a dull pain coming on from time to time in the lower right abdomen. It does not persist and lasts only for a minute or two. He has complained of this distress frequently. No mass could be palpated. The old area of tenderness in the upper mid-abdomen is not present. No enlarged lymph glands in the groins, axillæ or elsewhere can be palpated. Spleen not enlarged. Liver at the costal margin. Nurse states that for about a week stools have been a dark brown. Stool examinations show occult blood. Blood examination shows a sharp drop: hemoglobin, 36 per cent.; reds, 2,840,000; leukocytes, 5600. Differential count: polynuclears, 74.5 per cent.; large mononuclears, 2.5 per cent.; small mononuclears, 20.5 per cent.; transitionals, 2.5 per cent.; eosinophiles, 0; basophiles, 0; myelocytes, 0; no nucleated reds.

October 6. Examined patient today. Having all stools saved. The stools are lighter and have lost the dark brown color of a few days ago. Put an ice-bag again over the abdomen. The patient has evidently had more bleeding, which is now quieting down.

October 10. Stools are still lighter. Have still a greenish color. Dark brown color has disappeared. Patient complains of ill-defined distress in the upper abdomen. Calls it indigestion. Says it shifts from one point to another. Says it comes on after eating. Belches gas and it disappears.

October 16. Patient is not doing so well. Seems more prostrated and weak. Color is paler. Stools are much lighter, a pale green, but still contain blood by the benzedine test. Blood examination shows hemoglobin, 23 per cent.; reds, 3,184,000.

October 29. Patient is again better. His color is not so pale. The pain in the mid-back, which he has had for a number of days, has disappeared. Palpated the abdomen but could feel no mass. Stools still contain blood. Blood examination shows hemoglobin, 37 per cent.; reds, 3,232,000.

November 18. Examined Mr. G. H. today. Is doing fairly well. His color is better. Has gained some in weight. Complains very little of distress in the upper abdomen. Is eating a fairly general diet without distress. Stools are a typical milk stool, but show occult blood. Went over the abdomen carefully, but could palpate no mass.

December 16. Saw this patient today. Is doing splendidly. Color is improving. Is eating a fairly general diet, including fish and bacon and scraped beef, without distress. Blood examination is better: hemoglobin, 42 per cent.; reds, 4,016,000.

January 6, 1918. Patient is having distress in the upper abdomen, with belching of gas. Thinks it is due to sweetbreads which he had eaten. Has been eating all kinds of foods without distress up to this time. Stools are again a dark brown color and give a stronger benzedine test.

January 8. Patient was seized with a severe attack of vomiting in the night. Vomited, two or three times, a large amount, 500 to 1000 c.c. The material was a typical coffee-ground vomit. In spite of the fact that he took little fluids large quantities of dark material continued to come up. There was no tenderness in the abdomen. A marked succussion sound was present over the stomach area. The vomited material was acid, contained free hydrochloric acid, 12; total acidity, 34; no lactic acid; was strongly positive for blood by benzedine.

January 11. Patient today vomited a large amount of dark, grumous, black material, depositing a heavy sediment of small dark blood-clots on standing. Some of the last of the vomited material coming up contained bright blood. The vomited material was acid; contained free hydrochloric acid, 4; total acidity, 36; no lactic acid. Strongly positive benzedine test.

January 13. Patient is doing badly. Continues to vomit about 1000 c.c. of dark coffee-ground material four or five times a day. The vomiting attacks come in spells. Is taking plenty of fluids, and when the stomach becomes filled begins to vomit. Vomited material has no fecal odor. The vomiting, however, is of the obstructive type, as the stomach can be seen to slowly fill up with fluids and then empty itself, only to be filled again. Patient is rational, his pulse is good and the supply of fluid by rectum relieves his thirst.

January 17. Patient is losing ground. Vomiting still continues, all of a coffee-ground character, and in large amounts. He is becoming weak and prostrated. Anemia is marked. Patient is perfectly rational and is in no severe pain. The vomiting gives him relief.

January 19. Patient died today in coma. Vomited coffee-ground material only a few hours before his death.

With the completed clinical picture of the disease before us, one of two interpretations seems justified in a man aged seventy-four years, showing a high-grade anemia, with blood persistently in the stools, a hyperacid gastric content, no palpable mass, and dying with the symptoms of obstructive vomiting—namely, either a carcinoma high in the intestinal tract below the stomach or a duodenal ulcer with a carcinoma superimposed, causing obstruction by occlusion of the bowel. The diagnosis of the case prior to autopsy was a duodenal ulcer, with carcinoma superimposed, producing a slow-developing occlusion of the intestine not far from the pyloric opening.



Primary carcinoma of the duodenum. A, carcinoma; B, duodenal walls.

POSTMORTEM REPORT. (By E. T. Bell, M.D., Professor of Pathology, University of Minnesota.) Autopsy limited to an abdominal incision. No evidence of disease in the peritoneal cavity. At the lower curve of the duodenum and extending over into the third portion a resistant mass was palpated. The stomach and upper part of the duodenum showed a moderate degree of distention.



Upon opening the duodenum a tumor mass was found situated mainly in the third portion and in the lower part of the descending portion. The lumen was almost completely occluded by a cauliflower-like growth growing from the median and posterior wall. This growth extends from a point 2 cm. below the papilla of Vater to a point 9 cm. below the same structure, the length of the tumor in the long axis of the duodenum being therefore 7 cm. The greatest height of the growth projecting into the lumen of the duodenum is 3 cm. At a point 4.5 cm. below the papilla of Vater the lumen of the duodenum is extremely narrowed, being almost completely obstructed. The point of attachment of the cauliflower-like growth to the inner posterior wall of the duodenum measures 4 cm. There is no involvement of the head of the pancreas, which lies in contact with the portion of the duodenum from which the tumor is growing. There is no enlargement of the lymph nodes in the abdominal cavity at any point.

Microscopic examination of the tumor shows a typical adenocarcinoma of the papillary type. Infiltration extends deep into the muscular layer of the duodenum on its inner aspect.

The kidney shows numerous coarse pits over the surfaces, particularly marked along the convex borders. There is, however, only a moderate reduction in the amount of renal cortex. Microscopic examination shows the lesion to be of the coarse arteriosclerotic type. There is no anatomical evidence suggestive of renal insufficiency.

No gross or microscopic lesions in the adrenals, liver, pancreas or lymph nodes around the celiac axis.

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**REPORT ON THE EXAMINATION AND TREATMENT OF  
SOLDIERS INFECTED WITH HOOKWORM AT  
CAMP BEAUREGARD, LA., MARCH 1 TO  
SEPTEMBER 1, 1918.**

BY DONALD J. FRICK, MAJOR, M. C., U. S. A.,

THIS report is made for the purpose of showing the wide distribution of hookworm among Southern troops, the necessity of early examination and intensive and repeated treatment.

On account of a number of unavoidable circumstances, the examination for hookworm was not begun until the end of February, 1918. As the work was new to nearly all concerned, it was slow and not systematic. As a result, rather a large number escaped having their stools examined. After the examination was made and the list of positive cases fully determined, it was most difficult to get the men sent to the Base Hospital for treatment. The hospital had plans made to treat 100 cases every forty-eight hours, but was

hardly ever able to get more than 50, and sometimes only 15 or 20. As a result many men were sent overseas or to other camps before their turn came for treatment.

All examinations and treatment have been done practically since March, 1918, and the figures here given are for that time. The soldiers from which the statistics were gained were from the 39th Division and from troops sent in from time to time to fill out the division, several large contingents having been withdrawn for different purposes.

Table I shows the total number examined, with the positive cases and the percentages. The percentage of positive cases for all white troops was 11.5 per cent.; the percentage of positive cases in the colored troops was 1.1 per cent., a remarkable disparity and one that can be explained only by the fact that the negroes do not live in the hills where there is sandy soil, but come from the delta region.

TABLE I.

No. of cases.	From.	States.	Color.	Number positive.	Percentage positive.
18,390	39th Division	Louisiana, Arkansas and Mississippi	W.	2423	13.7
4,235	May draft	Louisiana, Arkansas and Mississippi	W.	365	9.0
2,217	Camp Pike	Missouri, Kentucky and Arkansas	W.	85	4.0
100	Camp Pike	.....	C.	2	2.0
1,407	July 29 draft	Louisiana	C.	16	1.1

The percentage of positive cases from these three States, Louisiana, Arkansas and Mississippi, was 12.3 per cent. Unfortunately we have no record of the actual number of cases that were positive from each State, so we cannot give figures for them separately; we can get an approximate idea from the cases treated.

Of the 2891 positive cases 1621 have been treated once and about 50 cases twice. These cases were sent in at random and probably fairly well represent all the organizations examined.

The three principal States gave the following figures: Louisiana, 898 cases; Mississippi, 454 cases; Arkansas, 243 cases; from all other States, 126 cases.

As the 39th Division, from which most of these figures were taken, was apparently about one-half from Arkansas and one-quarter from Louisiana and Mississippi, the high rate of infection in Louisiana is shown.

The first 1100 cases taken into the hospital were thoroughly examined and histories taken. From the tabulations of these statistics the figures for the rest of this paper are drawn. As there was no attempt at system in sending these cases into the hospital they well represent conditions in the troops at Beauregard.

There were 1100 cases studied and tabulated, as follows:

Louisiana, 64 parishes, 537 cases; Mississippi, 81 counties, 325 cases; Arkansas, 74 counties, 181 cases; other States, 57 cases.

The parish or county from which each infected soldier came was ascertained. The prevalence of hookworm in all three States is best shown by a review of these figures:

Louisiana, 64 parishes: 6 parishes gave 0 cases; 22 parishes gave from 1 to 4 cases; 36 parishes gave from 5 to 122 cases.

All four corners of the State and the middle were represented, the parishes along the Mississippi River yielding very few cases; 15 parishes, not counting Baton Rouge and Orleans, yielding 24 cases, less than 2 per parish. This condition prevails in the river counties of Arkansas and Mississippi:

Mississippi, 81 counties: 8 counties, 0 cases; 38 counties, 1 to 4 cases; 35 counties, 5 to 31 cases.

The cases were distributed throughout the State as in Louisiana:

Arkansas, 74 counties: 8 counties, 0 cases; 66 counties, 1 to 11 cases.

The small number of cases in all parts of Arkansas as compared with Louisiana and Mississippi is very striking.

The cases from all other States are listed below simply to show the necessity of hookworm study in all Southern camps.

#### STATES.

Alabama	12
Texas	23
Missouri	3
Oklahoma	1
Tennessee	4
Georgia	7
North Carolina	3
California	2
Virginia	1
South Carolina	3
	<hr/> 59

TABLE II.

The natural supposition that more farmers are infected than men with other occupations is shown by these statistics to be true, although all occupations, skilled and unskilled, seem to be touched by it.

Farmers	671
Lumber industry	78
Clerical	66
Miscellaneous	79
Mechanics	51
Students	48
Railroad men	42
Carpenters	22
Salesmen	17
Druggists	3
Musician	1
Butchers	2
Hostler	1
Lawyers	3
Bakers	5
Teachers	10
Factory workers	6
Total	<hr/> 1100

TABLE III.

The description of the kind of houses was not of much avail except to show the large number of box and log houses still occupied by these men, with the imaginable surroundings.

Frame houses . . . . .	831
Box houses . . . . .	227
Log houses . . . . .	36
Brick houses . . . . .	5
Tent . . . . .	1
	<hr/>
	1100

TABLE IV.

From the proved fact that water may be contaminated the source of water supply has interest. The 86 using city water, the 72 using artesian water and the 96 who had bored wells were the only ones that were immune from this source of infection.

Well (kind unknown) . . . . .	422
Well (open) . . . . .	163
Well (bored) . . . . .	96
Cistern . . . . .	88
City water . . . . .	86
Spring water . . . . .	73
Artesian water . . . . .	72
Pump . . . . .	62
Well (dug) . . . . .	17
River water . . . . .	16
No record . . . . .	1
Pond . . . . .	1
Condensed . . . . .	1
Tank . . . . .	1
	<hr/>
	1100

TABLE V.

The fact that nearly 70 per cent. came from a country that has a sandy soil corroborates what has been known before.

## CHARACTER OF SOIL.

Black . . . . .	88
Clay . . . . .	272
Sandy . . . . .	740
	<hr/>
	1100

TABLE VI.

The statement of 823 of these soldiers that there were no other cases in their family would hardly seem to point to the fact that it did not exist, but rather to the fact that diagnosis and treatment of hookworm have been very much neglected in these districts.

## NUMBER IN FAMILY WITH HOOKWORM.

Cases in family.	Number.
0 . . . . .	823
1 . . . . .	80
2 . . . . .	45
3 . . . . .	26
4 . . . . .	20
5 . . . . .	9
6 . . . . .	1
7 . . . . .	2
8 . . . . .	3
9 . . . . .	3
10 . . . . .	1
11 . . . . .	1
12 . . . . .	1
No record . . . . .	85
	<hr/> 1100

TABLE VII.

The high average of intelligence of these cases makes the answers of more value and shows the absolute neglect and disregard of the disease; 72 per cent. of these men had had seven years or more of schooling; 20 per cent. had four years in the high school or better.

## GRADE REACHED IN SCHOOL.

Grade.	Number.
0 . . . . .	48
1 . . . . .	11
2 . . . . .	27
3 . . . . .	42
4 . . . . .	66
5 . . . . .	55
6 . . . . .	71
7 . . . . .	142
8 . . . . .	140
1 year, H. S. . . . .	120
2 years, H. S. . . . .	80
3 years, H. S. . . . .	95
4 years, H. S. . . . .	142
College . . . . .	61
	<hr/> 1100

TABLE VIII.

Wearing shoes evidently follows education, as shown by the figure below. These men, however, are not far enough away from the period when all males go barefooted to make these figures important.

## NUMBER OF CASES WEARING SHOES ALL THE TIME.

Yes . . . . .	763
No . . . . .	337

TABLE IX.

These men were of average cleanliness, apparently, so their infection could not be placed upon a basis of lack of care of their skin.

## BATHS PER WEEK.

No. baths.	Men.
1 . . . . .	1 every two weeks
1 . . . . .	120
2 . . . . .	430
3 . . . . .	371
4 . . . . .	85
5 . . . . .	18
6 . . . . .	15
7 . . . . .	68
No record . . . . .	4

TABLE X.

700 took baths in places safe from contamination; the other 400 certainly courted infection through bare feet when bathing.

## BATHS, WHERE TAKEN.

Bath tub . . . . .	650
Creek . . . . .	276
River . . . . .	85
Shower . . . . .	49
Pool . . . . .	14
Lake . . . . .	12
Salt water . . . . .	11
Pond . . . . .	9
Spring . . . . .	2

To get an idea of the degree of disability caused by this disease, the men were scrutinized closely and any symptoms that might be due to the disease were tabulated.

1028 of these men were healthy, fine specimens of manhood.

72 looked pale, weak and listless.

66 had had diarrhea at times through life.

1034 None.

233 had had indigestion at times.

877 had none.

347 had had headaches.

753 had none.

633 acknowledge having had ground itch.

467 had never had it.

Of these men 172, or 15 per cent., had had typhoid fever, giving some evidence of their sanitary surroundings.

219 of the cases of hookworm had been diagnosed before coming into the service.

TABLE XI.

Hemoglobin estimation is interesting, as it shows what little effect the infection has had on the majority of this group. Unfortunately the laboratory only had time to make the estimation on 612 cases.

## HEMOGLOBIN.

No.	Cases.
60 . . . . .	2
70 . . . . .	44
80 to 85 . . . . .	364
86 to 90 . . . . .	158
91 to 95 . . . . .	28
96 to 100 . . . . .	16

TABLE XII.

The eosinophile count seems to verify the fact that an increase in the percentage is, in the majority of cases, found in hookworm. Counting 1 to 3 per cent. as normal, the height of the count apparently bears no relation to the severity of the case as judged by the condition of the patient. Those having an eosinophilia of 26 to 40, all were noted as healthy and only 1 had a hemoglobin of 70 per cent.; all the others were 80 per cent. or more.

## EOSINOPHILES.

No.	Cases.
1 . . . . .	9
1 to 3 . . . . .	310
4 to 6 . . . . .	440
7 to 10 . . . . .	171
11 to 15 . . . . .	80
16 to 20 . . . . .	55
21 to 25 . . . . .	17
26 to 40 . . . . .	18

**TREATMENT.** A routine was followed from the beginning and carried through without variation. The soldiers were sent to the Base Hospital in groups of 20 to 135, usually after the noon meal. Early in the afternoon they were given a dose of salts; at 5 P.M. a thin broth; at 6.30 P.M. more salts. The next morning at 6 A.M. a third dose of salts. At 8 A.M. and 10 A.M., 1 c.c. of oil of chenopodium. This was followed an hour later by an ounce of castor oil in orange juice. In the middle of the afternoon they were given some liquid nourishment and at 5 P.M. a full meal. The next morning, after breakfast, they were returned to their companies.

Of the 1100, 307 had slight vertigo and 154 pricking in the hands and feet; 32 were either retained to be treated in hospital or sent home in the ambulance. The remainder marched back the three or four miles to their companies.

The oil of chenopodium was purchased in bulk and poured into capsules or given on sugar.

The result of the treatment and its efficacy cannot be established, as only 435 of the cases were reexamined. Of these 84 were found positive, giving us an apparent sterilization of 80 per cent. in these cases.

The following method of collecting and examining hookworm specimens was used in the latter part of this work and found satisfactory.

1. A roster in duplicate is furnished the laboratory by the company commander through his medical officer, both of which are numbered serially and the original returned to the company commander, who directs the specimens to be collected in paraffin-paper sputum boxes. Each box has on it the serial number taken from the roster, corresponding to the name of the man who is to furnish the specimen in it. The specimens are then collected by companies, placed in boxes and delivered to the laboratory. A rubber band should be placed around each box to prevent it from coming open.

2. A test-tube (10 mm. x 10 cm.) is slipped under the rubber band of each box after having had placed on it the serial number of the box to which it is attached. Each specimen now has its individual test-tube.

KOFOID AND BARBER METHOD OF HOOKWORM EXAMINATION. (MODIFIED BY CAPTAINS BIRGE AND HENDERSON). 1. Fecal specimens collected in paraffin-paper sputum boxes numbered with roster of men, arranged in order.

2. Flotation of ova is accomplished by stirring a portion of feces (portion about the size of a small acorn) in a test-tube (10 mm. x 10 cm.), with concentrated brine, with a wooden stick, and let stand a few minutes until the debris sinks; the ova float.

3. With a wire loop, about 5 mm. in diameter, lift the surface of the concentrated solution and place on a slide for microscopic detection of the ova. No cover-glass is necessary. The ova are best seen with the condenser removed.

4. All intestinal parasite ova float near the surface of the portion placed on the slide and are easily found.

5. This method of examining for intestinal parasite ova has been very satisfactory.

CONCLUSIONS. 1. Hookworm is present in a large percentage of the soldiers from the South.

2. The colored soldiers of Louisiana show a remarkably low incidence of infection, less than 12 per 1000.

3. Hookworm apparently has no marked effect on the health of the great majority of these men. This may be due to the mildness of the infection or the fit condition of the men through training.

4. The early and repeated treatment of these cases is a necessity, so that they may not infect other localities, and because of the possibility that this infection may be a cause of lowering the soldier's resistance to other infections.

5. Treatment with oil of chenopodium is harmless and the routine suggested can be carried out anywhere that the men can be kept away from food.

6. On account of the better results shown in the Rockefeller Foundation Commission Report<sup>1</sup> by the use of milk in the morning and omission of purgatives, certain changes in our routine would be wise.

<sup>1</sup> Jour. Am. Med. Assn., February 22, 1918, pp. 499-507.



PLAN FOR EXAMINATION AND TREATMENT OF HOOKWORM CARRIERS IN SOUTHERN CAMPS. 1. A field laboratory will be established in the detention camp where all recruits are held in quarantine, this laboratory to be equipped to handle from 500 to 1000 stools per day. The men for this work may be detached temporarily from the Base Hospital.

2. The roster of each company in this detention camp will be sent to the laboratory. On the second day after the recruits are mobilized, stools of companies as designated by the commanding officer of this camp will be sent in, properly labelled, with the names of the men. The stools will be checked against the roster and opposite the names; after the examination is made the findings will be placed.

3. As soon as one hundred or more cases are found positive, these men will temporarily be confined to quarters for thirty-six hours and given the treatment.

4. All soldiers so confined should have at 4.30 P.M. clear broth; at 6 P.M. salts and another dose of salts at 5.30 A.M. the next day. At 6 A.M. a glass of milk. At 8 A.M. and 10 A.M. 1 c.c. of oil of chenopodium will be given. Castor oil, one ounce, or salts at 12 M. Soup at 2.30 P.M. and the regular meal in the evening.

5. From day to day all positive cases should be treated until all recruits with positive stools have gone through with the above routine.

6. One month after the first examination and treatment the laboratory shall send the roster of all names of soldiers who were found positive to the division surgeon, who shall order the stools of these men collected and sent to the laboratory of the Base Hospital for examination.

7. The names of all those having positive stools on the second examination will be sent to the division surgeon, who will have all these men mobilized to be sent to a field hospital or the Base Hospital for another course of treatment.

8. Upon the success of this plan, as shown by percentages cured, must rest the future treatment of these cases.

9. The advantages of this plan are: (a) Simplicity; no special material needed. (b) No loss of time, as the men will be in quarantine and only beginning training. (c) The assurance of getting all the stools. (d) The assurance of being able to treat all positive cases once. (e) The benefit to the men of getting rid of most of their parasites, which should help raise their resistance to other diseases. (f) A large decrease in the number of days in the hospital for every man with hookworm; therefore a better sick record for the camp.

NOTE.—Full credit is to be given Major James B. Guthrie, who inaugurated this work; to Lieutenant Joel B. Eastman and Lieutenant McNeese, for the collection of data and taking of histories. The laboratory work has been directed throughout by Captain E. G. Birge and Captain R. C. Henderson.

**GRANULAR TUBERCULOUS CONJUNCTIVITIS TREATED BY  
INSTILLATIONS OF TUBERCULIN.<sup>1</sup>**

BY ROBERT C. PATERSON, M.D.,

SARANAC LAKE, N. Y.

THE following case is reported to call attention to a method of treating a subacute tuberculous condition of the conjunctiva which, so far as I know, has not been previously employed except by Ellis and Gay,<sup>2</sup> whose article came to my notice after treatment had been inaugurated. This case also demonstrates the beneficial effects of controllable focal reactions produced by tuberculin on tuberculous tissues.

**CASE HISTORY.** C. S., male, clerk in a shipping office, aged twenty-three years. Has had symptoms of pulmonary tuberculosis since the early summer of 1916. Examination of the chest shows a marked infiltration of the right upper and middle lobes and to a lesser extent in the lower part of the left upper lobe. Tubercle bacilli were present in the sputum. There is some involvement of the larynx, with marked hoarseness, for the past eighteen months. Although he has had hemoptysis on several occasions, the course of the disease has been one of slow improvement. In May, 1917, the patient first noticed that the left eye was inflamed, and pain, which was severe enough to keep him awake at nights, was felt in the eye and forehead. Reading increased the pain; there was little discharge and the lids were never glued together in the morning; there was no photophobia; vision was said to be somewhat blurred; there was no fever associated with this condition. I first saw the patient early in August, 1917, at which time the inner part of the left bulbar conjunctiva and the part below the cornea were covered with pale, sluggish, trachoma-like granulations, which were also present on the conjunctival surfaces of both eyelids, especially the lower. There was some injection of the conjunctival vessels; no ulceration was present and there were no definite tubercles. The cornea was not involved. There was no enlargement of the preauricular lymph nodes. A small amount of mucoid secretion was present, but this was not marked. Cultures from the conjunctival sac revealed staphylococci and a large Gram-positive bacillus. The condition failed to respond to the ordinary eye washes and astringents. With the approval of Dr. E. R. Baldwin, who agreed that the condition was probably tuberculous, on August 17, 2 drops of a 0.00001 dilution of O. T. were instilled directly into the left conjunctival sac. No reaction followed this, and on August 21, 2 drops of 0.0001 O. T. were instilled likewise without reaction. On August 24, 2 drops of

<sup>1</sup> Read before the American Climatological and Clinical Association, June 5, 1918.

<sup>2</sup> *Lancet*, August 4, 1917, No. 4901, cxciii, 156.

0.001 O. T. were instilled and 2 drops of this same solution were again introduced four days later, no reaction following in either case. On September 6, 2 drops of 1 per cent. solution of O. T. were instilled into the left conjunctival sac, and this was followed by a sharp local reaction, characterized by increase in the pain during the evening of the day on which the instillation was made by marked increase in the amount of secretion, which became thick and yellowish, causing the eyelids to stick together. There was marked dilatation of all the conjunctival vessels and swelling of the conjunctiva and lids. This reaction passed off within forty-eight hours, by the end of which time the conjunctiva appeared clearer and the granulations were smaller than before the treatment. Ten days later a similar dose, namely, 2 drops of 1 per cent. solution, was instilled and almost immediately a dilatation of the conjunctival vessels could be seen and a sharp reaction followed, as in the former instance. This treatment was continued for six doses, at about ten-day intervals, making in all eight treatments, with reactions, after which the conjunctiva showed little evidence of disease. All symptoms had entirely disappeared, and at the time of writing the only evidence of previous disease is a few fine granulations and slight reddening of the bulbar conjunctiva at the extreme inner canthus. The palpebral conjunctiva is clear, but there seems to be some thickening, as the palpebral slit is slightly narrower than that of the opposite eye and the patient is not able to open the affected eye quite as widely as the right. The lung condition and throat disease have been quiescent during the treatment and have not been affected by the reactions. The patient is now doing light office work for the first time in two years.

**DISCUSSION.** Tuberculosis of the conjunctiva is one of the rarer localizations of this infection and may occur in the form of (1) ulcers, including lupus; (2) miliary tubercles; (3) granulations, including phlyctenules; (4) pedunculated tumors. A full description of these various forms and a general discussion of the subject of tuberculosis of the conjunctiva has been given by Eyres<sup>3</sup> in the Hunterian Lecture of 1912. Although tubercle bacilli were not demonstrated and no histological study was made of the granulations, as I did not care to excise any of the tissue for fear an ulcer would result at the site of the wound if bacilli were present in the granulations, the case here reported is in all probability one of tuberculosis of the conjunctiva. The clinical features in this case closely resembled the picture seen in Parinaud's conjunctivitis, except for the absence of enlargement of the preauricular lymph nodes, which is usually present in this disease. Möllers<sup>4</sup> has reported 2 cases of Parinaud's conjunctivitis, in which he demonstrated the presence of tubercle bacilli in the granulations by animal inoculation, and in this report quotes the

<sup>3</sup> *Lancet*, May 18, 1912, No. 4629, clxxxii, 1319.

<sup>4</sup> *Veröffentlichungen der R. Kochsche Stiftung*, Heft 4, 1913.

previous work of Wessely and others, who had proved the tuberculous nature of this disease. In this case the ordinary local tuberculin tests would not have assisted in diagnosis, as a positive reaction would have been obtained from the infection in the lungs, and although a subcutaneous test might have produced a focal conjunctival reaction, its use was contraindicated, owing to the danger of a general reaction on the pulmonary condition. The characteristics of the conjunctival lesion, the resistance to ordinary treatment, the presence of extensive tuberculosis elsewhere in the body and the marked focal reaction to tuberculin, followed by recovery, appear to justify the conclusion that the condition was a tuberculous one.

There has been much discussion and confusion as to the nature of the tuberculin reaction and as to how tuberculin aids in the cure of tuberculosis. Certain facts about the action of tuberculin are known, and a great many have been assumed without proof or sufficient experimental confirmation. Among these latter may be mentioned the production of antibodies of one kind or another in the serum and the development of a condition akin to anaphylaxis. The first of the known facts is that tuberculin has not a primary toxic action, even when used in enormous doses, on normal animals or persons, that is, on animals free from tuberculosis. Hamburger<sup>5</sup> reports having given 500 mg. of O. T. subcutaneously, without producing any general effects, to a child, which had failed to react to a previous skin test and which could, therefore, be considered non-tuberculous. Krause, working in the Saranac Laboratory, administered 25 c.c. of watery extract of tubercle bacilli intravenously to a normal guinea-pig without ill-effects, except for a watery diarrhea lasting a few days and caused by the rapid increase in the amount of fluid in the body. It may therefore be repeated that tuberculin has no deleterious effect on normal animals. Secondly, the presence of anatomic tubercle alters the body in some way so that all the tissues acquire a hypersensitiveness to tuberculin. This allergic condition or hypersensitiveness disappears when the tuberculous focus is completely healed or removed from the body. Thirdly, tuberculin acts specifically on tuberculous foci themselves, causing an acute inflammation in and around them. These focal reactions may be seen in experimental animals, killed during a general tuberculin reaction, and also are observed clinically in cases of tuberculosis where the disease is capable of direct observation, as in laryngeal and skin tuberculosis. The hyperemia accompanying this focal reaction permits of a dissemination of substances whose nature is not yet definitely known, and the entrance of these substances into the systemic circulation produces what is known as the general tuberculin reaction. The focal reaction thus produced by tuberculin may be a source of danger if the reaction is so great as to

<sup>5</sup> München. med. Wehnschr., 9 Juni, 1908, No. 23, I, 1220.

lead to a dissemination of bacilli to previously healthy tissues. On the other hand, if these reactions are slight and controllable the result of the inflammation is a tendency to walling off of the diseased focus by fibrosis, which is what we know as healing. The immediate object of tuberculin treatment should therefore be the production of slight and controllable reaction around the focus of disease. While this is simple when thus stated, it is not so simple in practice, particularly in pulmonary cases, for we are here dealing with a multiplicity of small foci in varying stages of development, from early and recent cellular tubercles to older, more or less fibrous or caseo-necrotic tubercles, which will be influenced differently by the same dose of tuberculin. If we add to this difficulty the fact that our methods of observing and estimating the results clinically are relatively coarse and depend chiefly on the patient's subjective symptoms, the difficulties and chances of error in judging the effects of our dosage are apparent.

The case here reported shows the beneficial results of such focal reactions, and a clearing up of the granulations was noticeable after each reaction. In this case it would have been unwise to give tuberculin subcutaneously on account of the extent of the disease in the lungs, but fortunately the location of the disease in the conjunctiva permitted of direct application and direct observation of the results. As the reaction was purely local, the beneficial results cannot be attributed to changes in the serum nor to an alteration in the so-called general resistance of the system, but must be ascribed to local tissue changes. Whether a non-specific irritant, which would have produced an inflammatory reaction, would have brought about similar beneficial results cannot be stated or denied, as it was not tried, but the use of jequirity in granular eye conditions is an old method and might give grounds for the belief that this or other non-specific inflammation-producing remedy might have been equally efficacious.

### STUDY OF AN UNUSUAL GLYCOSURIA.

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THERE has previously been reported a type of glycosuria in which while glucose was constantly excreted there were no symptoms of diabetes, the amount of sugar in the urine bore little or no relation to the amount of carbohydrate ingested and the blood sugar was normal. Klemperer,<sup>1</sup> who first noted this condition, found it associated with

<sup>1</sup> Verhändl. der Ver. f. inn. Med., Berlin, 1896, xvi, 67.

the evidences of a mild nephritis, and so named it renal diabetes. Since then others<sup>2</sup> have published cases in which the nephritis was not present, so that the condition has also received the name of Diabetes Innocens or Renal Glycosuria. Following the introduction of new chemical methods requiring only a few centimeters of blood for each determination,<sup>3</sup> the subject of blood sugar has been intensively studied. Investigators have found by taking samples of blood at frequent intervals that in the normal individual the blood sugar reaches its lowest point after a night's fast and rises soon after taking carbohydrate food into the stomach. From a half to one hour after the introduction of 100 grams of glucose into the fasting stomach the blood sugar rises from the normal level of 0.08 per cent. to 0.11 per cent. to not over 0.15 per cent., and falls within one and a half to two hours to below 0.11 per cent.<sup>4</sup> In diabetes the beginning of the blood sugar curve is frequently much above 0.11 per cent.<sup>5</sup> while in milder and less understood types of carbohydrate disturbance it may lie within or below the normal limits.<sup>6</sup> When the blood sugar rises to a point between 0.17 per cent. and 0.18 per cent., even in the normal individual, glucose is excreted in the urine and this point is spoken of as the kidney threshold for glucose.<sup>4</sup> Renal glycosuria implies a lowering of this threshold while the blood sugar response to a carbohydrate meal is normal.

While the following case seemed in many respects to fulfil the requirements of a renal glycosuria, this diagnosis could not be made because the blood sugar curve was abnormal. At the same time the failure to follow Allen's paradoxical law<sup>7</sup> made it improbable that the case was one of true diabetes. On account of its peculiar relation to renal glycosuria and a true error of carbohydrate metabolism I have thought this case worthy of report.

**CASE HISTORY.** S. B., aged fifty-five years, a Polish Jew, entered the medical service of the University of California Hospital on May 17, 1918, and was discharged on June 8, 1918. He had syphilis at thirty-one and gonorrhea at thirty-four, with gleet for ten years afterward. Five weeks before admission he was seized with sharp substernal pain radiating down both arms and "into the teeth." There were no further attacks for one week, when they recommenced and grew steadily more frequent until he was having four or five in twenty-four hours. Sudden exertion brought on an attack

<sup>2</sup> Weiland, W.: Ueber einige Aetiologisch bemerkenswerte Diabetesformen, *Deutsch. Arch. f. klin. Med.*, 1911, cii, 167.

<sup>3</sup> Lewis, R. C., and Benedict, S. R.: A Method for the Estimation of Sugar in Small Quantities of Blood, *Jour. Biol. Chem.*, 1915, xx, 61.

<sup>4</sup> Hamman, L., and Hirschman, I. I.: Studies on Blood Sugar, *Arch. Int. Med.*, 1907, xx, 761.

<sup>5</sup> Mosenthal, H. O., Clausen, S. W., and Hiller, A.: The Effect of Diet on Blood Sugar in Diabetes Mellitus, *Arch. Int. Med.*, 1915, xxi, 93.

<sup>6</sup> Janney, N. W., and Isaacson, V. I.: A Blood Sugar Tolerance Test, *Jour. Am. Med. Assn.*, 1918, 70, xvi, 1131.

<sup>7</sup> Allen, F. M.: *Glycosuria and Diabetes*, Harvard University Press, 1913, 72.

which nothing seemed to relieve. The pain present on admission lasted all day and was worse between 10 A.M. and noon, when he vomited.

Examination showed no signs of syphilis and the Wassermann reaction was negative. Along the fifth rib from the heart's apex to the sternum there was during the cardiac cycle a distinct scratching sound which was interpreted as pericardial friction. He had a leukocytosis of 25,000, which diminished to 12,000 during his stay in the hospital. The blood urea nitrogen was 8 mgm. per 100 c.c., and the phenolsulphonephthalein excretion 70 per cent. in two hours. A reducing sugar was found in his urine, and this gave typical crystals of glucosazone with Cipollina's test. Aside from the question of his glycosuria the clinical diagnosis was syphilis, arteriosclerosis with coronary thrombosis and subsequent pericarditis.

On May 20, when sugar was found in the urine, the patient was put on a prescribed weighed diet. After a preliminary observation period of three days, when he excreted from 5 to 11 grams of glucose per twenty-four hours, food was withdrawn, with the expectation that in twenty-four hours the urine would be sugar-free. Much to our surprise there was still a trace of sugar after two days' starvation. Food was then given again, the amounts of protein and fat being kept at the same level while the carbohydrate was regularly increased until it approximated the amount found in a normal diet. Practically the same amount of sugar was excreted on this diet as on the first day after starvation. Antisyphilitic medication was continued during the patient's stay in the hospital, and he had no further pain.

The urinary findings and the diet given are shown in Table I.

TABLE I.

Date.	Volume.	Total N.	Urea N.	Amm. N.	Creatinine.	Glucose.		Acetone body.	Protein.	Fat.	Cho.	Liquid intake.	Naked weight.
						Gm.	%						
May 21	840	12.00	.....	0.894	1.048	11.05	1.50	..	70	70	75	1500	55.0
22	800	12.91	.....	.666	1.029	5.41	.67	0	70	70	75	1500	55.2
23	1000	18.18	12.65	.450	.962	8.62	.80	0	70	70	75	1500	55.4
24	1300	10.24	8.17	.564	.916	Trace	.....	0	0	0	0	3000	55.8
25	1360	17.00	11.13	.680	1.060	Trace	.....	0	0	0	0	3000	54.8
26	1421	15.28	12.74	.789	.943	7.40	.51	0	54	52	67	1320	54.6
27	1420	15.96	12.33	.947	.928	6.46	.45	0	69	70	75	1500	53.4
28	860	10.36	8.43	.811	1.025	14.33	1.60	0	66	53	67	1350	53.4
29	1300	13.00	8.97	.492	.856	7.22	.55	0	70	70	75	1500	53.4
30	630	7.00	4.69	.242	.561	3.94	.62	0	away	part	of day		
31	1040	8.82	7.25	.495	1.154	4.41	.43	0	59	68	123	1500	53.0
June 1	970	8.01	.....	.....	.....	5.05	.52	..	70	68	150	1500	54.4
2	1190	13.68	.....	.....	.....	5.36	.45	..	70	70	250	1500	54.2
3	1020	11.55	.....	.....	.....	7.23	.44	..	70	70	250	1500	54.6
4	1450	8.95	.....	.....	.....	3.25	.22	..	70	70	250	1500	54.6
5	1500	7.24	.....	.....	.....	4.44	.29	..	70	70	299	1500	55.0

The blood sugar curve following 100 grams of glucose given June 6 after a night's fast, with the diuresis and amount of sugar excreted, are shown in the accompanying chart.

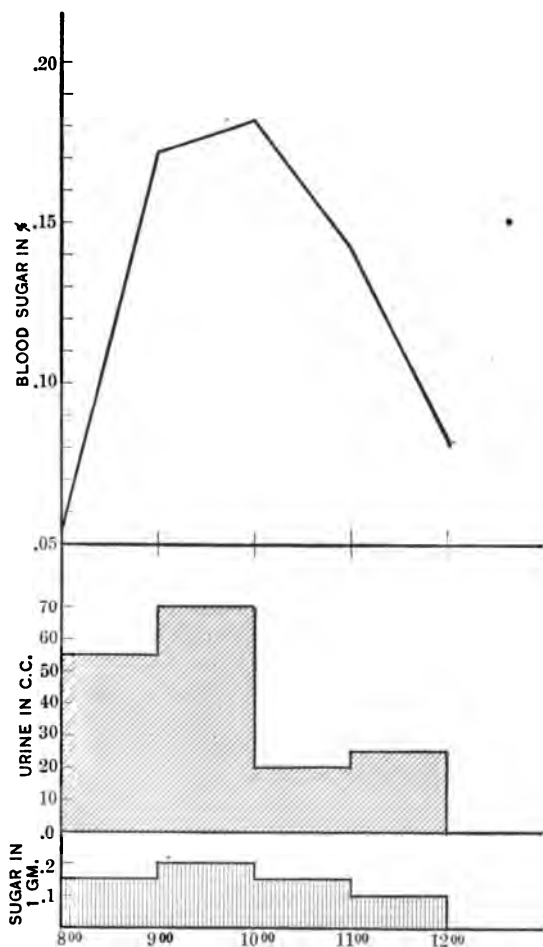


Table II shows the figures corresponding to the chart.

TABLE II.

Time.	Blood in sugar.	Urine in c.c.	Sugar in gms.
8 A.M. . . . .	.0566	464	
9 . . . . .	.1705	54	.166
10 . . . . .	.1807	70	.215
11 . . . . .	.1415	20	.166
12 . . . . .	.0789	24	.100



Folin's direct Nesslerization method<sup>8</sup> was used for the urinary nitrogen, his Permutit method<sup>9</sup> for the ammonia, the method of Van Slyke and Cullen<sup>10</sup> for the urea in the urine and blood, Folin's method<sup>11</sup> for the determination of the creatinine, Benedict's method<sup>12</sup> for the quantitation of the urinary sugar and the method of Lewis and Benedict<sup>3</sup> for the blood sugar.

**SUMMARY.** There were no symptoms of diabetes. The daily amount of sugar excreted by this patient varied from a trace to 14 grams but bore no relation to the amount of carbohydrate ingested except during the fast days, when only traces were found in the urine. A night's fast on June 5 sufficed to make the urine sugar-free at 8 A.M. the following day. The blood sugar was below normal at this time, but after 100 grams of glucose increased to above the normal expected rise and did not return to normal until the fourth hour. The percentage of glucose in the urine varied from 0.22 per cent. to 1.5 per cent., and was inversely proportional to the amount of urine. Kidney function was normal so far as could be determined by the phenolsulphonephthalein excretion and the blood-urea nitrogen.

**DISCUSSION.** Independence of the glucose excreted from the carbohydrate in the diet is not consistent with true diabetes, as Allen has shown, and it was felt from this patient's response to increased carbohydrate intake on fixed amounts of protein and fat that his glycosuria would prove to be entirely dependent on a low kidney threshold. Although the kidney threshold was determined between points too far apart to be of value (0.05 per cent., and 0.17 per cent.), it may be supposed that it was quite low, because during the two fast days when the blood sugar would perhaps not be expected to rise very much above the fasting level of 8 A.M. on June 6 (0.05 per cent.), traces of sugar were still excreted. This lowered threshold would satisfactorily explain the presence of the small amounts of glucose constantly found in this patient's urine. But when 100 grams of glucose were given after a night's fast, the blood sugar curve was found to show a higher rise than the normal expected one and a delayed fall. This type of curve has been found associated with mild diabetes and with ductless gland disease, and apparently demonstrated some abnormality of carbohydrate metabolism. We may suppose that this individual would have excreted a small amount of glucose only when the curve reached its highest point if

<sup>8</sup> Folin, O., and Denis, W.: Nitrogen Determination by Direct Nesslerization, *Jour. Biol. Chem.*, 1916, xxvi, 473.

<sup>9</sup> Folin, O., and Bell, R. D.: Applications of a New Reagent for the Separation of Ammonia, *Jour. Biol. Chem.*, 1917, xxix, 329.

<sup>10</sup> Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urease and its Use in the Determination of Urea, *Jour. Biol. Chem.*, 1914, xix, 211.

<sup>11</sup> Hawk, P. B.: *Practical Physiological Chemistry*, P. Blakiston's Son & Co., 1916, 506.

<sup>12</sup> Benedict, Stanley R.: The Detection and Estimation of Glucose in Urine, *Jour. Am. Med. Assn.*, 1911, lvii, 1193.

the kidney threshold had not been low, so that the blood sugar response was not concerned with the glycosuria.

CONCLUSION. A case of glycosuria with apparently lowered renal threshold for glucose is reported.

There was evidence of abnormal carbohydrate metabolism.

True diabetes was probably not present.

### THE GRAHAM-STEELL MURMUR IN MITRAL STENOSIS.

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IN a number of cases of mitral stenosis there is heard at the left of the sternum in the region of the pulmonic valves, about the third intercostal space, a soft blowing diastolic murmur (Graham-Steell murmur). This has been ascribed to insufficiency of the pulmonic valves, due to dilatation of the pulmonic ring. Cabot<sup>1</sup> found this murmur in 22 out of 50 cases coming to autopsy, but on postmortem examination no recognizable lesion of the aortic or pulmonic valves was observed and no dilatation of the pulmonary artery. Thayer, on the other hand, in the discussion following the reading of Cabot's paper, states that when there was an opportunity of examining the heart after death he found in all cases with the Graham-Steell murmur marked dilatation of the right ventricle, with dilatation of the pulmonic ring.

The question which has interested us in a study of a rather large number of cases of mitral stenosis is in what proportion of cases this so-called Graham-Steell murmur is heard and what are its characteristics, so that there may be little difficulty in recognizing it. The Cardiovascular Board at Camp Jackson, consisting of four regularly appointed well-trained men and four men of exceptionable ability loaned for this work by Major Arthur E. Davis, of the 156th Depot Brigade, were instructed to refer to me all cases of mitral stenosis as well as all individuals of the draft who showed a snappy first sound at the apex, and all those who had a diastolic murmur, no matter where it was located, for detailed study. It was due to their painstaking care and hearty coöperation that a series of 36 cases of mitral stenosis were studied. These cases were definitely mitral stenosis and not aortic insufficiency, with a Flint murmur, although the differentiation may be at times difficult. This question will be made the subject of a subsequent communication.

Of the 36 cases, 24 were pure mitral stenosis, *i. e.*, with no insufficiency, and 12 were associated with a definite systolic murmur of an insufficiency. In the 36 cases a diastolic murmur along the left border of the sternum was heard 12 times, or in 33.3 per cent. of the

<sup>1</sup> Tr. Assn. Am. Phys., 1914, xxix, p. 22.



These numbers are rather small to permit of definite conclusions, but it is apparent that in our cases of mitral stenosis hemoptysis, when it occurred, was found more frequently when a Graham-Steell murmur was present.

The interest attached to the Graham-Steell murmur lies in the fact that it makes the differential diagnosis between aortic insufficiency with a Flint murmur and a mitral stenosis with a Graham-Steell murmur a matter of some difficulty. In searching for the murmur it is recommended that the patient be examined in various positions, in various phases of respiration and before and after exercise.

### ON THE USE OF A BINOCULAR LOUPE FOR THE EXAMINATION OF THE FUNCTIONAL TROUBLES OF THE PUPIL.

BY DR. EMIL BERGER,

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It is a well-known fact that the iris is influenced by the different organs of the body, and particularly by the nervous system. The Swiss physiologist, Maurice Schiff (Geneva), therefore, rightly considers the iris as the esthesiometer of the human body. The examination of the functional troubles of the pupil are consequently of greatest importance not only for the ophthalmologist and neurologist, but also for medical science in general. Therefore the greatest interest has been shown toward experimental methods regarding functional troubles of the pupil. Such is the case particularly in respect to the reaction of the pupil to impressions of light.

Thirty years ago medical men examined this function by means of lighted matches, held before the eye of the patient; others used candlelight for this purpose or observed whether the darkening of the eye, caused by the hand being held before the eye and then withdrawn, influenced the size of the pupil. In present times the light-reaction of the pupil is tested by means of an electric pocket lamp. There is, however, still needful a more perfect method for observation of the functional trouble of the pupil. In the well-known manual on the relationship between ophthalmology and general medical science, Schmidt-Rimpler has already pointed out the utility of the binocular microscope for that purpose. In those times, however, the binocular microscope was a very expensive and unhandy instrument, for which reason it was not adaptable nor generally used by medical science. During the year 1899, Prof. J. Lippmann,<sup>1</sup> of the Academy of Science in Paris, demonstrated a very much simpler binocular loupe, and this has been recorded in the *Précis*

<sup>1</sup> Compt. rend. de l'Acad. des Sciences de Paris, November 23, 1899.

*de physique biologique*, by Prof. J. Weiss<sup>2</sup> and in the French *Encyclopaedia of Ophthalmology*.<sup>3</sup> I have in no way influenced the introduction and use of my binocular loupe in medical science, which employs it particularly in ophthalmology, dermatology and anatomy; it is chiefly Prof. Haltenhoff (Geneva), who has published a paper<sup>4</sup> on this subject. Having perceived, however, that one of the most important uses of my binocular loupe, that is, the examination of the functional troubles of the pupil, has been overlooked by physicians, I consider it my duty to correct this omission by this short communication. I hope that soon the general use of the binocular loupe will take place. The observer will, however, bear in mind that such an examination has always to be performed at the maximum of the focus. I believe that the binocular loupe will be generally employed, all the more as the latest improvement of stereoscopic spectacles can be made at a very low price,<sup>5</sup> and therefore is accessible to all.

The change of form of the pupil is very distinctly visible on being examined with this loupe. I have examined such changes of form of the pupil very thoroughly in the Hospital of Prof. Charcot (Salpêtrière) in Paris, and the results of my researches were communicated by Prof. Brown-Séquard in the Parisian Academy of Sciences (1888). In cases of *tabes dorsalis* the pupil frequently appears oval and symmetrical in both eyes with a large and slanting diameter of the ellipse. These changes already take place in the beginning of *tabes dorsalis* and can be attributed to the nerve trouble of the vessels of the iris. The changes of form are not infrequently transitory (Buhmke).

Besides this there are other changes in the form of the pupil, which are caused by partial atrophy of the iris, appearing in consequence of functional troubles of the peripheric neuron. These changes of form take place at the later period of *tabes dorsalis* and are there stationary. The latter change of form of the pupil can be ascertained with the binocular loupe and is indicated by indistinctness of the irregularities of the surface of the iris, in the non-atrophied part of which protuberances and depressions are visible through the binocular loupe. These changes in the pupil likewise manifest themselves in cases of general paralysis (Talko).

By the aid of my stereoscopic magnifying lenses it is easy to ascertain the Argyll-Robertson symptom (pupilar contraction of convergence and the absence of these with impressions of light) and the

<sup>2</sup> Paris, Masson & Cie, editors, 1905.

<sup>3</sup> *Encyclopédie Française d'Ophthalmologie*, t. v., Paris, Doin & fils, 1905.

<sup>4</sup> Haltenhoff's de l'emploi en ophthalmologie de loupe binoculaire de Berger, *La Clinique Ophthalmologique*, 1905.

<sup>5</sup> By the optician Charles Hitchling, at Geneva, 29 quai des Bergnes, for the price of 7 francs. I hope that also in the United States the opticians will construct these stereoscopic spectacles, which are very useful for diamond cutters, watchmakers, miniaturists, naturalists, etc.

Gowers symptom, which precede the symptoms of Argyll-Robertson. The symptom of Gowers consists in oscillating movements of the iris in reaction toward light impression.

Many cases of tabes dorsalis in which examination with the naked eye leads to the conviction of the absence of pupillar reaction toward light has proved, when examined with the binocular loupe, that the pupil still showed tardy and passing contractions toward light impressions. It is likewise possible to recognize the symptom of Gowers by the use of the binocular loupe much earlier than with the naked eye. The binocular loupe is also very useful for the observation of the consensual reaction of the pupil toward light and the Pilez-reflex (pupillar movement by closing of eyelids).

I hope that this communication will contribute to awaken interest for further investigation of functional trouble of the pupil by means of the binocular loupe and so verify my researches, as also to perfect them by and through new researches.

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### **EPIDEMIC CEREBROSPINAL MENINGITIS AT CAMP BEAUREGARD, LA.**

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PLAQUEMINE, LA.,

AND

WILLIAM H. HAMLEY, LIEUTENANT, M. C.,

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FROM November 10, 1917 to June 1, 1918, we had 126 cases of epidemic cerebrospinal meningitis, with 65 recoveries and 61 deaths, a mortality of 48.26 per cent. A review of these cases disclosed certain facts as to the transmission, forms of the disease, symptomatology, treatment and complications which may be of interest.

**TRANSMISSION.** Our experience leads us to believe that the patient, ill of the disease, as a disseminator of the infection is not dangerous, especially after active treatment has been instituted. Of many throat cultures taken upon admission and during the course of the disease, only one culture in one patient proved suspicious. Not one of the officers, nurses or enlisted men constantly in the wards during this period contracted the disease, although during November and December no precautionary measures, such as the wearing of masks or the use of sprays, were taken. The enlisted men particularly were careless in their handling of and close personal contact to patients. We have still to look upon the carrier as the dangerous agent to others only, for we have no record of any carrier who developed the disease.

**FORMS AND SYMPTOMATOLOGY.** Three forms of the disease were noted: the ordinary (frank and masked), the fulminating and the chronic forms. The ordinary form presented itself either as a frank meningitis with premonitory symptoms, as headache, loss of appetite, malaise and later chill, fever, vomiting, intense headache, painful stiffness in the muscles of the neck, great sensitiveness to noise, hyperesthesia, photophobia and the usual signs of meningitis, or as a masked meningitis with the symptoms-complex of influenza or laryngitis, chilly sensations, fever, general malaise, headache, pains in bones, hoarseness, cough, sore-throat, etc. This last form during the prevalence of influenza presented at first a perplexing problem, more easily solved later when a careful inspection for the typical petechial eruption very often present in these cases gave us a clue. One case, correctly diagnosed only on the third day of the disease, presented at the onset a typical picture of acute articular rheumatism. One symptom, noticed in most of these masked cases, never proved misleading, a "slow mentality;" patients were slow to answer questions, showed an aversion to being disturbed and wanted to be let alone. This symptom always justifies a lumbar puncture. A leukocyte count is always helpful and will often suggest the diagnosis. One of our first cases showing indefinite symptoms was correctly diagnosed before puncture upon a leukocytosis of 56,000.

The eruption in our experience has been helpful as a diagnostic point, being present in almost 50 per cent. of our cases as a whole, and in the last series, when carefully looked for, in 80 per cent. It appears first on the shoulders, forearms, legs and chest as petechiæ, erythema or rose-colored hyperemic spots in the ordinary form of the disease and as typical hemorrhagic spots of varying size in the fulminating forms or in very severe infections. We were so impressed with the value of this eruption as a diagnostic sign that it was our invariable rule to inspect carefully all patients presenting any suspicious symptoms. It was also noticed that these spots came on quickly, sometimes in a few hours, necessitating frequent inspections.

The fulminating form, of which we had 10 cases, proved how powerless we are in the face of this most dreadful disease. We include under this form only those cases which died within twenty-four hours of the onset. Five of these died within twelve hours. The onset was usually sudden, with violent chills, headache, great depression, fever, vomiting, slow, feeble pulse, hyperexcitability, followed by unconsciousness and delirium. Kernig's and later signs of the disease usually were not present. Two cases upon admission presented no definite symptoms and the disease was suspected only when unconsciousness supervened, a lumbar puncture in both yielding clear fluid under pressure with no organisms. Autopsy in both cases revealed only congestion of the meninges, a positive diagnosis being made on culture of the spinal fluid after death. One case lived six and a half and the other eight and a half hours after

the appearance of the first symptoms. Another case was brought in, showing profound depression and overwhelming intoxication, a hemorrhagic eruption appearing within three hours of the first symptom, quickly spreading over the whole body, with death in ten hours. Spinal fluid, clear, showed meningococci. Fluid and blood culture were both positive. The other cases presented no unusual symptoms except profound depression and a general expression of being acutely and desperately ill, with no improvement whatever under treatment.

We had 2 cases of the chronic form, the typical long-drawn-out cases of preserum days. One case, actively treated three times during the space of seventy-five days by the intraspinal, intravenous and intraventricular routes, finally died of hydrocephalus, due to blocking. It is but fair to state that the injection of serum into the lateral ventricles was done as a last resort. The other case recovered after a three months' siege of the disease.

Two cases developed a postmeningitic septicemia, both after an actively treated meningitis by the intravenous and intraspinal routes, blood cultures in the first case giving a meningococcus growth on the thirty-sixth day and the second on the sixteenth day of the disease. The first case had seven lumbar punctures, with 280 c.c. serum and three intravenous doses, 180 c.c. serum, ran a typical course until the nineteenth day, when the temperature, normal for five days, assumed an intermittent type, normal in the morning to 103° to 104° in the afternoon, after a daily chill, to return to normal in a few hours. The patient felt well between paroxysms and was up and about. Physical and blood examinations revealed nothing to account for the fever. On the thirty-fifth day a petechial eruption was noticed. On the thirty-sixth day a blood culture gave a meningococcus growth. The intravenous treatment was again instituted, the patient showing very severe anaphylactic reaction. On the forty-third day he developed an acute endocarditis. On the forty-seventh day blood culture was negative. On the sixtieth day the patient was well.

The second, another typical case, rather severe, did well under intravenous and intraspinal treatment up to the sixth day, when the temperature went up to 104.6°, developing physical signs of pneumonia, lobar. On the seventh day a blood culture gave a growth of pneumococci; a type differentiation, Avery's method, showed Type I. Antipneumococcic serum 100 c.c. intravenously on the seventh and again on the eighth day brought the temperature to normal, with general improvement in pneumonic condition. On the tenth day the temperature again went up to 105.6°, with cloudy spinal fluid. Blood cultures negative to pneumococci and meningococci. Active treatment, both routes, again instituted. On the twelfth day a blood culture again was negative. Temperature ran an up-and-down course, evening and morning, with the patient getting worse. On the



sixteenth day a hemorrhagic eruption appeared, quickly spreading over the whole body, particularly thick and marked on the hands, forearms, shoulders, face and legs, some spots being 2 cm. in diameter with a periarticular inflammation of the wrist and ankle-joints. Blood culture gave a meningococcus growth. Up to this day he had received 15 intraspinal doses of serum, 600 c.c., and 5 intravenous 300 c.c. Active treatment was continued up to the day of death, the twenty-first day, when, realizing the futility of these methods, an injection of 20 c.c. of serum into the lateral ventricles and the subdural space was resorted to as a last measure. It is rather difficult to offer any explanation of the blood-stream condition in these two patients after active treatment unless we theorize in the first case upon the flaring up of a latent focus of infection, and in the second the breaking loose of a walled-off focus never reached by the serum, reinfecting cerebrospinal system and the blood stream.

**TREATMENT.** It is not necessary at this day to argue and present statistics as to the value of serum treatment in epidemic cerebrospinal meningitis. It is conceded that a potent polyvalent serum, used in a systematic manner, is not only the accepted method of treatment but a specific. Major Flexner states that "the serum acts locally upon the meningococcus and upon the exudate, and in this way arrests the infection and promotes subsidence of the inflammation and restoration of the damaged membranes. To effect this it must be brought in direct relation and kept in continuous contact with the seat of the infection and in high concentration. Now, since the serum does not reach the meninges, normal, and less so the inflamed, from the blood, it is useless to inject it subcutaneously or intravenously in the expectation that it will find its way into the subarachnoid space."

Our experience has led us to the conclusion that the disease is a blood-stream infection, with local manifestations in the cerebrospinal system. The great percentage of cases showing the eruption when carefully looked for, 80 per cent. in the last series, and the great percentage of positive blood cultures when our laboratory facilities were adequate, forced us to this conclusion, and as a practical consideration we are justified in formulating our treatment upon such a theory. Therefore, to bring the serum in contact with the meningococcus, we use it in the blood stream, *i. e.*, intravenously, and in the subarachnoid space simultaneously. At the first puncture, unless there was positive evidence from the quantity, character and pressure of the cerebrospinal fluid that the disease was not epidemic cerebrospinal meningitis, 40 c.c. serum was administered after draining as much fluid as possible. If no untoward symptoms, such as intense headache, supervened the head of the bed was elevated to facilitate drainage. The serum was introduced by gravity only at an elevation of twelve to fifteen inches. Elevating the foot of the bed facilitated the introduction of the serum. The use of the

syringe and pressure was discarded altogether; 1 c.c. serum was then given subcutaneously for desensitizing purposes. In one to one and a half hours 60 c.c. serum diluted in an equal quantity of 0.6 per cent. saline solution was given intravenously. This was repeated every twenty-four hours for three doses unless some indications existed for its continuation. In severe infections 100 c.c. was given and repeated at closer intervals. In view of the fact that we had two cases of postmeningitic septicemia and several cases of blocking and reinfection from foci, and knowing that large doses of serum intravenously, repeated at frequent intervals, are well tolerated and practically harmless, we would recommend the larger dose at eighteen- or even twelve-hour intervals in all cases as a routine measure, in the hope of preventing these disastrous postmeningitic conditions and complications. The serum is not given with a view of reaching the subarachnoid space and acting locally upon the meningococcus in the cerebrospinal fluid, but to destroy the organisms in the blood and to prevent local complications in various organs, eyes, ears, heart, joints, etc. Lumbar puncture with a 40 c.c. dose of serum was repeated every twelve hours until the temperature reached normal. This was about the fifth or sixth puncture, at which time the fluid was generally clearing up. Lumbar puncture and the same dose of serum were repeated every twenty-four hours for a number of days, equal to one-half the number of punctures and serum injections it required to bring the temperature to normal, about three or four in the average case. The fluid was then found clear, with a predominance of lymphocytes in the cell count. Another spinal puncture was made in forty-eight hours and serum administered or not according to the appearance of the fluid and the general indications. On the fourth or fifth day after this last puncture another was made as a precautionary measure. In the average case the fluid was clear, with a slightly increased cell count, largely lymphocytes, and the patient convalescent. The temperature, after reaching normal about the fifth or sixth serum injection, often rose daily about four hours after each treatment. This rise is generally due to the serum, and in the management of our cases at this period we did not consider the temperature. Kernig's rigidity and retraction will in most cases be aggravated between the third and fifth day of treatment. As a rule this is due to the irritating action of the serum on the cerebrospinal system. Headache will also be more intense an hour or two after the serum injection. These signs and symptoms we generally neglected also, so that the management of our cases ultimately narrowed down to fluid findings.

From an analysis of fluid findings in many cases we have formulated the following, which represents the character of the fluid in the average case from day to day: At the first puncture the fluid may be clear, slightly cloudy, depending upon the duration or severity of the disease. Clear fluid in a positive case will show an increased

globulin content and a greatly increased cell count, mostly polynuclears and no organisms. This fluid will be cloudy on the second or, at the latest, the third puncture, when organisms may be found. If fluid is cloudy it will show many pus cells or leukocytes and generally organisms. These, however, may not be found on first puncture.

On second day: Fluid is more cloudy, contains more pus cells; organisms are generally found.

On third day: Fluid clearing up slightly and color changing to pale yellow or straw color; many polynuclear leukocytes staining well; no organisms as a rule.

On fourth day: Fluid clearing up, straw color; leukocytes, polynuclear, less abundant, staining well.

On fifth day: Fluid light straw color; few healthy leukocytes, polynuclears, some degenerating, poorly staining ones, and a few lymphocytes.

On sixth day: Fluid almost clear; few polynuclears and a preponderance of lymphocytes. In our experience, when the lymphocytes predominate in the cell count and the polynuclears show poorly staining qualities, the case is progressing satisfactorily and the twenty-four-hour puncture is discontinued.

To show the results of serum intravenously we have divided our cases into three series:

I. Those treated without serum intravenously, 83 cases, with 38 recoveries and 45 deaths; mortality, 54.2 per cent.

II. Those treated with serum intravenously late in the disease, 9 cases, with 4 recoveries and 5 deaths; mortality, 55.5 per cent.

III. Those treated intravenously on admission, 34 cases, with 23 recoveries and 11 deaths; mortality, 32.3 per cent.

Comparing figures in I and III shows the value of early intravenous treatment. However, comparison between I and II is not quite fair to the intravenous method for the reason that 8 of these 9 cases were very ill, almost hopeless, the method being used as a last resort. The fact that 4 of these cases recovered demonstrates the value of this procedure even late in the disease.

Other therapeutic measures: Hot baths, 112° to 115°, used in 39 cases, were found of distinct value to allay restlessness, clear up delirium and induce sleep. The duration of the baths was from five to fifteen minutes. Morphine hypodermically was used freely, and, in our opinion, is indispensable. The bromides, aspirin, sulphonal, trional, etc., were found absolutely useless. Bright light and noise were distinctly harmful and tended to make patients restless and wakeful. It was often noticed that when one patient in the ward became noisy, the others also soon became restless, irritable and noisy. One patient in series I, apparently in a dying condition, was tided over by a hot intravenous injection of 0.6 per cent. saline solution, 250 c.c., and ultimately recovered. The subsequent use of this measure in three other cases did not show such happy results.

Lumbar puncture in the first half of our cases was always done under chloroform anesthesia. Realizing the possible bad effect of the drug used once or twice daily over an extended period, we abandoned it for local anesthesia, subsequently used altogether except in the case of delirious and unmanageable patients. A 2 per cent. cocain solution, 0.5 c.c. under the skin, anesthetized it sufficiently to make the skin puncture painless. The ligaments and deeper tissues did not prove very sensitive in most patients, for very few complained of pain unless unusual difficulty was encountered in getting into the canal. Morphin sulphate, gr.  $\frac{1}{4}$  hypodermically, was always given twenty minutes before a lumbar puncture under local anesthesia.

Four needles were broken, the accident occurring in delirious patients who became unmanageable, the needles already in the canal snapping off as the patients struggled to get away from the orderlies who held them.

COMPLICATIONS. All cases did not run a typical course. Some progressed satisfactorily up to the tenth, fifteenth or even twentieth day, when all symptoms reappeared, temperature, headache, vomiting, rigidity, retraction of the neck, irregularity or dilatation of pupils, slight occasional delirium, etc. Spinal fluid which had cleared up became cloudy again, with findings very similar to the first days of the disease and organisms. This occurred in cases having had active treatment and can be explained only by the breaking loose of a walled-off focus in some inaccessible place in the cerebral sub-arachnoid space, disseminating meningococci throughout the whole cerebrospinal system.

Blocking is another serious complication in the course of the disease. We understand by the term blocking the closing up by the exudate of the communication between the cerebral and spinal subarachnoid spaces at the base of the brain. This condition is generally due to one or more of three factors: insufficient treatment early in the disease; serum, in sufficient quantity, not reaching every portion of the subarachnoid space and ventricles, or treatment instituted late in the disease.

Blocking usually occurs late in the disease. It may, however, occur early, one of our cases blocking in forty-eight hours. This case presented an unusually severe infection. Symptoms may develop rapidly, as in this case, in six to eight hours, or may come on so gradually as to barely arouse suspicion until no fluid can be drained from the spinal canal. When the clinical picture of the disease does not improve under treatment it is well to be on guard. Headache, slow mentality, semicoma, delirium, vomiting, unequal pupils, nystagmus, early changes in retina and optic nerve suggestive of choked disk, a difference in note in auscultatory percussion of lateral ventricles, a gradually diminishing amount of cerebrospinal fluid changing from a pale yellow to a deep golden-yellow color, with few

cells, generally lymphocytes, and later a dry puncture, should establish a reasonably certain diagnosis.

In the presence of these complications the intraspinal and intravenous routes of medication offer very little hope of getting the serum in contact with the seat of the disease. The direct introduction of serum into the lateral ventricles and under the dura at the base of the brain is our only hope. Intraventricular puncture through a trephine opening in the skull was done in 5 cases, 3 of blocking and 2 for recrudescence, with 1 recovery, a case of blocking. This patient presented a severe form of the disease and had a rather stormy time under intraspinal and intravenous treatment until the eighteenth day, when temperature went up with aggravation of all symptoms, the spinal fluid diminishing in quantity and showing a deep yellow color. On the twenty-first day the patient had intense headache, was semidelirious, restless and generally worse; right eye showed marked internal strabismus; outlines of optic disk hazy; small bloodvessels of retina abnormally large and prominent; lumbar puncture dry. Up to this day the patient had received three intravenous, 180 c.c., and 18 lumbar punctures, 730 c.c. serum. On the twenty-second day lumbar puncture again dry. No improvement whatever. The left lateral ventricle was punctured through a trephine opening just below the left parietal eminence, some cloudy fluid drained and 10 c.c. serum was introduced in the ventricles and 10 c.c. under the dura. On the twenty-third day the general condition was the same: Left facial paralysis, right hemiplegia and aphonia. On the twenty-sixth day the patient was quiet and seemed to understand when spoken to. Intraventricular puncture through the same trephine opening, 45 c.c. clear fluid removed, 10 c.c. serum introduced. Fluid examination showed globulin double plus, considerable debris and some lymphocytes. On the thirtieth day the patient was able to move the right leg. On the thirty-first day, lumbar puncture, 70 c.c. clear fluid drained. Fluid examination showed a thin transparent coagulum, some debris and a few lymphocytes. No serum given. On the thirty-fifth day paralysis and aphonia had disappeared. Recovery thence uninterrupted. Our results, while not brilliant, are encouraging when we consider the gravity of the condition for which this operative procedure was undertaken.

Most of our cases developing these complications had an ample quantity of serum early in the disease, so that we are more inclined to consider the serum not reaching every portion of the subarachnoid and the cerebral ventricles as the responsible factor. Just why this condition should obtain in some cases we are unable to state, and so far having no means of determining this point early, it is our opinion that in very severe infections and in cases not progressing satisfactorily after a week or ten days of active treatment early intraventricular injection of serum is justifiable.

**Serum reaction:** We had 3 cases of very severe anaphylaxis, 2 in cases who had had serum three and five weeks previously, and 1 upon the first intravenous injection where the desensitizing 1 c.c. of serum was inadvertently omitted. The first symptom noticed was flushing of the face and chest, quickly spreading over the whole body, with sensation of heat, followed by choking sensation, dyspnea, restlessness, severe chill, unconsciousness, cessation of respiration, a fast weak pulse and later high temperature followed by profuse sweating. The condition of these patients was alarming but improved under adrenalin hypodermically and artificial respiration. One case of late serum sickness was interesting in that it presented symptoms very similar to postmeningitic septicemia, differentiated only upon a negative blood culture. The case ran a typical course until the ninth day, when temperature, normal for three days, went up to 101° and a profuse general urticaria appeared over the whole body. Up to this day he had had seven lumbar punctures, 280 c.c., and three intravenous doses, 180 c.c. serum. On the seventh day spinal fluid was almost clear, with 60 per cent. lymphocytes. On the tenth day fluid was clear, showing nothing special. On the fourteenth day the eruption assumed a morbilliform appearance all over the body, less marked on the face, with intense itching and temperature of 102.4°. Spinal fluid clear. On the nineteenth day the eruption was distinctly hemorrhagic, the spots being the size of a split pea, with pain and swelling of the joints. Blood culture was negative. On the twenty-sixth day the skin was clear and the patient convalescing.

**END-RESULTS.** The end-results of our 65 cases discharged from the hospital as cured have not been very encouraging. Two were discharged on a surgeon's certificate of disability, one for manic-depressive insanity, existing prior to meningitis, the other for complete deafness, a sequel of the disease. Twenty-two cases now in the hospital, suffering from various pains and aches, stiffness of back, legs, etc., all classified as "postmeningitic neuroses," are apparently unable to do duty, and as far as we are able to determine at present will never be of much service. Of the remaining forty-one who are apparently well it is impossible yet to judge how many will be able to stand up under hard work, for it has been our experience that most cases did fairly well until put to the test of hard drills and long hikes. The severity of the disease does not seem to have any bearing upon the ultimate condition. The case of postmeningitic septicemia apparently is in as good condition as any other, full of energy, active, doing duty. One of the mildest cases who recovered under three punctures and two intravenous doses of serum is suffering as much as the case of blocking and intraventricular punctures. We are tempted to believe that there may be an element of malingering in some. We have seen what we designate as the "postlumbar puncture neurotic," in our opinion a malingerer. We have had in the

hospital three such patients, punctured once or twice as meningitic suspects, who complained as much as the chronic case who had a three months' siege of the disease with twenty-five lumbar punctures. The true evaluation of the malingering element is the problem which confronts us now. However, we have no doubt that the majority really suffer and are disabled, although with our present means of diagnosis we are unable to detect any pathological lesions to account for their condition.

The work here reported was done in the service of Major James B. Guthrie, and we desire to thank him for allowing us to analyze it. Credit should be given to the following officers: Captains Ward, Dorsett and Steele and Lieutenants Zuercha, Ruka, Sharp and Bell, who were connected with the service and carried on the care and treatment with the compilers of this report.

### **INFLUENZA-PNEUMONIA CASES SHOWING GAS IN FASCIAL TISSUES.<sup>1</sup>**

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DURING the epidemic of influenza-pneumonia at Camp Dix a number of cases have shown peculiar accumulation of gas in the fascial tissues. Twelve such cases have been studied as closely as the exigencies of a crowded service would permit. Three of the cases have recovered. A total of twenty were reported.

Gas first made its appearance in the subcutaneous tissue at the base of the neck anteriorly and laterally and over the upper portion of the chest, from the clavicle to about the third rib. While this was the usual location two cases have shown a more extensive distribution of gas. In one case gas was found also in the subcutaneous tissue of the cheeks, eyelids, mesial aspect of the entire right arm and in small areas over the sides of the chest and abdomen and in the flanks.

During life the patients showed a slight ballooning of the skin over the affected areas. These areas were distinctly crepitant, the gas disappearing from the immediate region of the palpating finger on pressure. A notable feature is that the skin over the ballooned area

<sup>1</sup> Extract from a paper read before a meeting of the Medical Society of the County of Kings, Brooklyn, N. Y., October 15, 1918.

felt cold to the touch while the neighboring tissues were feverish. There was no perceptible change in color of the tissues in the affected areas.

The patients with this accumulation of gas have shown no related subjective symptoms, and no symptoms of an intercurrent infection. There has been no discoloration of the affected areas. No edema, no congestion and no induration or other signs of infection have been observed. It has not been associated with any other especially characteristic symptoms or physical signs. The accumulation of gas has apparently not affected the course of the disease. It appears to be an inert gas in the tissue spaces. The affected tissues gave a crackling sound on pressure with the stethoscope. In one case, Lieutenant John J. Young, M. C., of Ward No. 37, records "over the precordium rales very similar to sounds elicited with moderate pressure of stethoscope over emphysematous cutaneous tissue." At autopsy the mediastinal connective tissue was distended with gas in this case.

**POSTMORTEM FINDINGS.** Three of the cases described have come to autopsy. The pathological findings were not those of cases dead of infection with *Bacillus aërogenes capsulatus*, nor in fact did the lesions present the characteristics of an infection.

In the three subjects which came to autopsy the distribution of the gas has likewise varied in extent. In the most pronounced case the gas was distributed in the subcutaneous fascia as follows: over the upper anterior portion of the chest as far laterally as the axilla, continuing upward over the front of the neck and laterally as far as the anterior border of the trapezius muscle, over the parotid region, over both cheek areas and eyelids. Similarly it could be felt in the vascular sheaths of the right axillary, brachial and radial arteries as far as the base of the thumb. Within the chest the fascia of the anterior and posterior mediastinum appeared as a reticular tissue distended with gas and bearing more or less fatty tissue. Gas was also found beneath the pleura at the hilum of the lung and in the smaller septa of the lung. In the last-named situation small gas vesicles were seen especially frequently at the edges of the small septa passing inward from these. In no case was gas observed within the muscle sheaths, and the muscles were firm and normal in appearance.

On section the superficial gas-containing fascia of the neck appeared distinctly whitish. The bloodvessels appeared to contain less blood than those elsewhere. There was no discoloration, no fluid, no infiltration or other signs of pathological change. There was no particular odor to the affected tissue and neither the liver nor any other internal organ gave any evidence of gas accumulation.

**BACTERIOLOGY.** Small bits of the gas-containing fascia were removed for inoculation on various solid and liquid media. These were incubated both aërobically and anaërobically. In no case was



a growth obtained. No bacteria were found in the smears made directly from the excised and crushed gas-containing tissue.

SUMMARY. 1. Those cases of influenza-pneumonia at Camp Dix which showed gas in various fasciæ showed clinically no evidence of an intercurrent infection.

2. Three gas cases ran an uneventful course and recovered without surgical procedure.

3. At autopsy the gas-containing tissue showed little blood in the vessels. It presented no discoloration, no congestion, no induration or other signs of inflammation.

4. Bacteria were not recovered.

5. Gas was not found within the muscle sheaths.

6. In the gas cases coming to autopsy the air-containing alveolæ appeared emphysematous in the more nearly consolidated lung lobes.

7. The distribution of the gas corresponds with what we would expect to be the dissemination of gas escaping from the weakened alveolæ of the lung under pressure.

8. We are of the opinion that the "gas" in the above cases of pneumonia is air from the lung which reaches its distribution as a result of purely mechanical factors. We do not believe the gas is of bacterial origin.

## RENAL DIABETES.<sup>1</sup>

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THAT diabetes is not always a rapidly fatal disease has long been recognized by medical writers, the diagnosis being founded upon the chief sign of the disease, the persistent presence of sugar in the urine. In many cases this is the only symptom, the patients enjoy excellent health, the glycosuria persists and seems to be little influenced by diet, and, after years under observation, may remain unchanged or may entirely disappear. The association of the kidneys with the etiology of diabetes is not to be wondered at, especially from the 17th century, when Thomas Willis discovered that the pathological change in the urine was the presence of sugar, and Dobson, in 1775, demonstrated that the blood contained sugar before it appeared in the urine. One naturally conceived of a permeability point in the concentration of blood sugar at which the

<sup>1</sup> Read in part before the Society for Experimental Biology and Medicine, May 17, 1916, Proceedings, xiii, 153.

kidney tolerance would be overcome and sugar would escape into the urine. In the ordinary cases of diabetes it was observed that the urine sugar varied more or less directly with the diet and the patient's tolerance was estimated by the amount of carbohydrate that could be ingested without producing glycosuria. The question arose whether one was dealing with a condition in which this permeability point was lowered by organic or functional kidney changes or whether the kidneys were unaffected and the symptoms due to a constitutional defect in carbohydrate metabolism. Early writers, as Galen, Aetius of Amida and others, considered it to be a kidney disease. Theophrastus Patrocelus, however, described it as a constitutional disease showing itself in marked pathological changes in the urine. In 1878 Claude Bernard,<sup>2</sup> by very imperfect methods, demonstrated that an excess of sugar in the blood was the direct cause of glycosuria.

Von Mering's<sup>3</sup> demonstration of phlorizin glycosuria in 1886 raised the question as to whether a like condition occurred clinically in man, a state in which the kidney permeability point to sugar was so lowered that glucose appeared in the urine in the presence of a subnormal or normal blood sugar. In 1896, Klemperer<sup>4</sup> reported a case which he styled "Renal Diabetes" and stipulated that for such a diagnosis one must have the following postulates fulfilled:

I. That the glycosuria should be within wide limits independent of the amount of carbohydrate in the food.

II. That the sugar in the blood should at least not be increased but should rather be diminished.

III. That the development of a nephritis decreases the glycosuria.

Schupfer,<sup>5</sup> in criticism, pointed out the fact that although a complicating nephritis usually causes a lessening or cessation of a mild glycosuria, in other cases no change can be found and claimed this to be the case in arteriosclerosis complicating diabetes. Luthje<sup>6</sup> in 1901 claimed that in order to make the diagnosis one must ascertain that the glycosuria develops as a direct result of a nephritis, that the blood sugar be below normal and that no relation exists between the blood sugar and the extent of the glycosuria. In 1908 Bonniger<sup>7</sup> questioned the diagnosis made in all previous cases as the blood sugar estimations were based upon the reducing power of whole blood. This, he said, gave us erroneous values as he was under the impression that blood corpuscles contained very little sugar. Tachau<sup>8</sup> further decorated the diagnostic requisites by

<sup>2</sup> *Leçons sur le diabète*, Paris, 1878, 75.

<sup>3</sup> *Verhandl. d. Cong. inn. Med.*, Wiesbaden, 1886, v, 185.

<sup>4</sup> *Verein f. innere Med.*, Berlin, 18 Mai, 1896.

<sup>5</sup> *Il Policlinico*, 1900, vii-m, 1.

<sup>6</sup> *München. med. Wchnschr.*, 1901, xlviii, 1471.

<sup>7</sup> *Deutsch. med. Wchnschr.*, 1908, xxxiv, 780. *Verhand. d. Cong. f. inn. Med.*, 1913, xxx, 178.

<sup>8</sup> *Deutsch. Arch. f. klin. Med.*, 1911, civ, 448.

stipulating that the glycosuria, in addition to being completely or in a great degree independent of the diet, must persist upon a diet free from carbohydrates and that it be not greatly increased, following the ingestion of large amounts of sugar.

Von Noorden<sup>9</sup> claimed that blood sugar estimations must be the deciding factor, and in this connection, Frank,<sup>10</sup> in 1910, again brought up Bonniger's criticism of whole-blood estimations. Jacobsen,<sup>11</sup> in 1913, published some very interesting data on alimentary hyperglycemia and glycosuria. He found that one hour following the administration of 100 grams of glucose the hyperglycemia had passed off in most of the cases examined and the blood sugar test at this time showed only a very slight increase. He pointed out that this is probably what happened in the cases diagnosed as renal diabetes.

De Langer,<sup>12</sup> in 1914, stated that to make a diagnosis of renal diabetes the glycosuria need not be uninfluenced by the diet and pointed out that in phlorizin diabetes the urine sugar is greatly influenced by ingested carbohydrates.

Galambos,<sup>13</sup> in the same year, differentiated between mild diabetes mellitus and renal diabetes as follows: "When a chronic glycosuria is present with but a questionable or no hyperglycemia, we have to do with either a diabetes mellitus with increased kidney permeability or with renal diabetes. When the blood sugar is slightly increased the case is one of diabetes mellitus with increased renal permeability. When, however, the blood sugar is subnormal or normal, or when alimentary hyperglycemia is absent, the case is one of renal diabetes. "Glycosuria largely independent of the diet speaks for renal diabetes."

Salomon,<sup>14</sup> also in 1914, cited the work of Porges, Leindorfen and Stresower and Frank as showing that an independent glycosuria with low blood sugar values can exist in patients showing no sign of kidney disease. He stated that renal diabetics excrete small amounts of sugar daily, 10 to 12 grams, and that this is uninfluenced by diet; also that 100 grams of glucose in the morning do not increase the sugar excretion.

The consensus of opinion seems to have been that renal diabetes was a condition in which the patient had none of the classical symptoms of diabetes mellitus but did have a low-grade glycosuria, little influenced by diet, and which was present at a time when the blood sugar was normal. In view of the fact that Lewis and Mosenthal<sup>15</sup> have but recently given an excellent review of the cases so far reported a repetition would seem out of place at this time.

<sup>9</sup> Die Zuckerkrankheit., Berlin, 1912, 527.

<sup>10</sup> Arch. f. exper. Pathol. u. Pharmakol., 1913, lxxii, 387.

<sup>11</sup> Biochem. Ztschr., 1913, lvi, 471.

<sup>12</sup> Berlin klin. Wchnschr., 1914, li, 1792.

<sup>13</sup> Deutsch. med. Wchnschr., 1914, xl, 1301.

<sup>14</sup> Johns Hopkins Hosp. Bull., 1916, xxvii, 133.

<sup>15</sup> Ibid., xl, 217.

In reviewing the cases, however, one is impressed by the fact that most of the diagnoses were based upon the observations that the patients had no diabetic symptoms and that the glycosuria seemed to bear no relation to the diet. When it came to actually determining the point of permeability to sugar and whether or not sugar was escaping from the kidney at the very time when the blood sugar was normal, little can be found to establish the diagnosis.

The case described by Gram<sup>16</sup> had a low glycosuria of from 0.4 to 0.6 per cent. at the time when synchronous specimens of blood contained 0.085 to 0.1 per cent. sugar. Lewis and Mosenthal<sup>14</sup> reported a case with a constant glycosuria in twenty-four-hour specimens, during a period of five days' starvation; blood tests made on the third and fifth days gave normal values (0.11 per cent.). The patient had no diabetic symptoms. We cannot draw conclusions from their synchronous blood and two-hour urine tests. The blood specimens were taken at a time when alimentary hyperglycemia had passed off, but the urine at that time would still normally have sugar as a result of the hyperglycemia.<sup>17</sup> Other blood specimens were taken just before eating and the synchronous urine specimens contained the alimentary glycosuria of from one to two hours.

Murlin and Niles<sup>18</sup> have described a case which they consider to be one of renal glycosuria. The patient, a man, aged twenty years, suffered from loss of weight, furuncles, polyuria, increased thirst and weakness. The daily excretion of glucose varied from 14.7 to 26.9 grams and bore no relation to the carbohydrate content of the diet, which varied from 14.9 to 100 grams. The blood-sugar estimations were made five hours after breakfast and gave normal values on several days. One day's starvation rendered the urine sugar-free. No synchronous blood and urine tests were made and nothing is known of the permeability point to sugar or of the nature or extent of alimentary hyperglycemia and glycosuria. The blood sugar findings are such as one would expect in mild diabetes.

The above case reported by Gram is certainly one of "glycosuria with normal glycemia," as Allen states it. Several other cases, including that of Lewis and Mosenthal and that of Bonniger, seem to approach this type, but the data from which to draw conclusions are insufficient. It is known that the blood sugar level when uninfluenced by diet or by glycogenolysis varies in different individuals, high levels being found in diabetes of long standing and in nephritis. So it would be quite possible for a nephritic whose blood sugar level is above 0.2 per cent. to have a glycosuria of renal origin which would not be dependent upon an increase of blood sugar in that individual. One of the cases about to be reported is of this type.

The value of the blood sugar method has frequently been brought

<sup>16</sup> Hospitalstidende, Copenhagen, 1915, lviii, 329.

<sup>17</sup> Frank: Ztschr. f. physiol. Chem., 1910, lxx, s. 129.

<sup>18</sup> Am. Jour. Sc., 1917, cliii, 79.

into question in deciding the type of the case. Bonniger's and Frank's criticism of whole blood estimations is not without foundation, as the sugar concentration of the plasma alone must be the deciding factor influencing the kidney cells. However, in the light of recent work,<sup>19</sup> this would tend to include more cases as renal glycosuria, since the corpuscles seem to have, as a rule, a slightly greater concentration of sugar than the plasma.

The following cases are reported as showing two distinctly different types of glycosuria which seem to be of renal origin. The blood sugar estimations were made by a modification of the Lewis and Benedict method already described.<sup>20</sup>

**CASE I.**—Mrs. M. B., an American housewife, aged thirty-one years, was admitted to the service of Dr. Quintard in the New York Post-Graduate Hospital on July 30, 1915. Case History No. 5356. She was sent to the hospital on account of an intractable glycosuria complicating pregnancy.

*Family History.* Mother died of "inflammation of the bowels." Father, aged seventy-four years, living and in good health. Two brothers and four sisters are living and in good health. Her family have all been of an extremely nervous temperament. No history of diabetes, obesity, gout, goitre, tuberculosis, gigantism or disorders of the kidneys, stomach or heart.

*Personal History.* Born in Westminster, Vermont, of old New England stock. She experienced poor health from early infancy and has always been poorly nourished. Her mother told her that when a child the urine was irritating, and that only by the best of care could the vulva be kept in a healthy condition. From early childhood she has had a weak stomach and suffered from severe attacks of indigestion. These attacks were usually accompanied by marked urticaria, especially so following the ingestion of fish. She has a peculiar susceptibility to the sting of the honey-bee. On one occasion, four years ago, she almost died from the effects of a sting. It was followed by nausea, vomiting, purging, loss of consciousness, marked edema and extreme weakness of pulse. Brisk stimulation brought about recovery in a few hours. Had chicken-pox when a child; catarrhal jaundice at the age of thirteen; normal menstruation began at fourteen; mumps when eighteen. Married at the age of twenty-three and two months later had a second attack of catarrhal jaundice. Her first child was born one and a half years after marriage. Early in the pregnancy she noticed burning, frequency and urgency of urination. Her physician found sugar in her urine and made a diagnosis of diabetes mellitus. Before this date (1908) her urine had never been tested for sugar.

*History of Present Illness.* Following the discovery of the glycosuria she was placed upon a restricted diet, but as this was followed

<sup>19</sup> C. V. Bailey: Proc. Soc. Exper. Biol. and Med., 1916, xiii, 153.

<sup>20</sup> Myers and Bailey: Jour. Biol. Chem., 1916, xxix, 147.

by a rapid loss of weight and extreme weakness it was soon abandoned. The patient returned to her usual diet and quickly regained both weight and strength. After two weeks the urine was again examined for sugar, which was present to the extent of 5 per cent., or about the same amount as before the restricted dieting. This glycosuria persisted throughout the pregnancy, which was otherwise uneventful. Her diet continued unrestricted, her weight increased to 150 pounds and she looked and felt in perfect condition. A baby girl, weighing ten and a half pounds, was delivered under ether anesthesia. An endometritis lasting three weeks followed the birth of this child. Recovery was good, and since that time the patient has been in fair health.

Four years ago another unsuccessful attempt was made to render her urine sugar-free, but was quickly abandoned, due to rapid loss of weight and extreme weakness. Since that time her diet has been unrestricted. Her appetite has always been good—never abnormal. She has not had increased thirst. The urine volume has been about 1500 c.c. She has had a distaste for sweet things, but is fond of fruit. She has always been undernourished, nervous and rather easily exhausted, but has been able to do all the housework for three adults and a child. In the past seven years there have been no subjective urinary symptoms. Her chief complaint has been of occasional attacks of indigestion, when she would suffer from headache, nausea, vomiting and epigastric distress. No hematemesis. Bowels regular. No constipation. Diarrhea at times. No blood or excess of fat in the stools. Menstruated regularly up to three months ago.

*Physical Examination.* Poorly nourished, symmetrical adult female of rather querulous temperament. The skin is very transparent; cheeks flushed; lips very red; veins of neck, chest and temples prominent; eyelashes long; slight seborrhea of scalp; pupils equal, regular and react well to light and accommodation; no exophthalmos; no widening of palpebral fissures; von Graefe's sign negative; corneal sensibility slightly decreased; upper and lower teeth missing; mucous membrane bright red; throat apparently normal; thyroid gland slightly enlarged, symmetrical and does not pulsate; no tremor of extended fingers; reflexes all present and active; no swaying on standing with feet together; no ataxia; chest symmetrical, subcostal angle acute, expansion equal and good; breasts enlarged, slightly tender and areolæ pigmented; examination of lungs reveals nothing abnormal; cardiac dullness extends to right sternal border; apex beat palpable in fifth intercostal space in midclavicular line; heart sounds normal—no adventitious sounds; arteries barely palpable; pulse 84, regular and equal; blood-pressure: systolic 110, diastolic 65; respirations 22; temperature normal; abdomen enteroptotic and flatulent; liver palpable at costal margin; upper pole of right kidney can be palpated; spleen not enlarged; bimanual examination reveals an enlarged uterus;

no abdominal tenderness or abnormal masses are present; no edema of extremities; hemoglobin 68 per cent. (Sahli); red blood cells 4,444,000; leukocytes 7900, of which 64 per cent. are polymorphonuclear; urine light straw colored—specific gravity 1047—and shows a slight trace of protein, acetone and diacetic acid, and sugar 5 per cent.; microscopically—a few hyaline and granular casts; phenolsulphonphthalein excretion on August 10, 1915, was 39 per cent. in two hours; on August 17 the excretion was 42 per cent. in two hours.

On August 3, 1915, her blood in the morning before breakfast showed 0.09 per cent. sugar, and the urine at the same time contained 1 per cent. sugar. A comparison of the blood and synchronous urine sugar is found in Table I, Case I. The effect of starvation upon her weight and excretion of sugar is shown in Table II, Case I, the patient at the same time being at rest in bed.

TABLE I.—CASE I.

Date.	Blood sugar. Per cent.	Synchronous urine sugar. Per cent.
Aug. 3, 1915 . . . . .	0.089	1.00
Aug. 5, 1915 . . . . .	0.110	1.60
Aug. 6, 1915 . . . . .	0.130	2.10
Aug. 11, 1915 . . . . .	0.098	3.10
Aug. 25, 1915 . . . . .	0.092	1.25
Oct. 13, 1916 . . . . .	0.116	8.40

This table simply shows that with normal blood-sugar values, sugar was constantly excreted by the kidneys. As the rate of excretion of urine is not known the relationship of sugar excretion to blood-sugar concentration cannot be expressed.

TABLE II.—CASE I.

Date.	Diet.	Weight. Pounds.	Glucose excreted. Grams in twenty- four hours.
Aug. 3, 1915 . . . . .	Regular	103	35.0
Aug. 5, 1915 . . . . .	Hunger	99	18.3
Aug. 6, 1915 . . . . .	"	96	14.7
Aug. 7, 1915 . . . . .	"	95	19.5

*Test of Alimentary Hyperglycemia and Glycosuria.* On the morning of August 11, 1915, synchronous blood and urine specimens were obtained, the patient being in the fasting state. She was then given 30 grams of glucose in 225 c.c. weak tea. Blood and urine specimens were obtained at frequent intervals for a period of six hours. The results are tabulated in Table III, Case I, and in Chart I, Case I.

It will be seen that the patient excreted glucose at the rate of 1.29 grams per hour when the blood contained 0.098 per cent. sugar. Alimentary hyperglycemia was slightly delayed and prolonged, as is found in mild cases of nephritis. Urinary excretion greatly increased on the subsidence of the hyperglycemia.

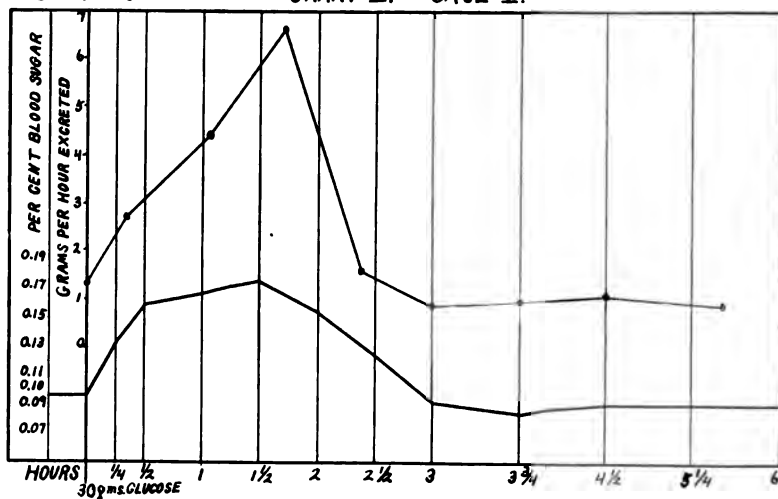
The greatly increased permeability of the kidneys to sugar is well shown at the one and a half hour period, when the rate of glucose excretion was 6.7 grams per hour while the blood sugar was at a point where normal kidneys just become permeable.

TABLE III.—CASE I.  
M. B., August 11, 1915.

Time..		Blood sugar. Per cent.	Urine.				Fluid intake. c.c.
A.M.			c.c. per hour.	Chlorides. Grams per hour.	Sugar.		
					Per cent.	Grams per hour.	
9.15	....	0.098	60.0	0.0460	3.120	2.000	
9.45	....	30 grams glucose.	44.0	.....	2.940	1.290	225
10.00	1/4 hr.	0.135					
10.20	1/4 hr.	0.159	58.0	0.1056	4.830	2.830	225
10.30							
10.45	1 hr.	0.168	.....	.....	.....	.....	225
11.00	1 1/4 hrs.	0.172	66.0	0.1450	6.660	4.398	
11.10							
11.15	1 1/4 hrs.	0.176					
11.45	2 hrs.	0.156	97.0	0.2180	6.750	6.700	225
12.15	2 1/4 hrs.	0.105					
12.25		.....	159.0	0.2540	1.040	1.650	
12.45	3 hrs.	0.093					
1 P.M.	....	.....	94.0	0.1690	0.952	0.897	
1.25	3 1/4 hrs.	0.086					
1.45	4 hrs.	0.088	150.0	0.2100	0.657	0.986	225
2.00							
2.15	4 1/4 hrs.	0.092					
3.00	5 1/4 hrs.	0.092	90.0	0.1400	1.219	1.097	
3.45	6 hrs.	0.092	84.0	0.1340	1.086	0.912	225

M.B. II-VIII-15

CHART I. CASE I.



The patient was put upon a mixed diet containing about 50 grams of available carbohydrate. Upon this diet her twenty-four-hour urine contained not more than 2 per cent. glucose while her normal weight was sustained. Her freedom from unpleasant symptoms, however, prompted her to return to unrestricted diet upon leaving



the hospital on August 25. In two weeks her weight increased twenty pounds. The second pregnancy was uneventful, and on January 28, 1916, she was delivered of a healthy baby weighing nine pounds, nine ounces. Glucose was constantly present in the urine.

In October, 1916, nine months after the birth of her second child, further tests in alimentary hyperglycemia and glycosuria were carried out. At this time the percentage glucose in her daily urine had greatly increased, being 7.4 per cent. on October 15, 6.94 per cent. on October 16, and 9.2 per cent. on October 17. On the morning of October 13, synchronous blood and urine specimens were obtained, the patient being in the fasting state. She was then given 30 grams of glucose in 400 c.c. of weak tea. Blood and urine specimens were obtained at frequent intervals for the succeeding six hours. The results are shown in Table IV, Case I, and Chart II, Case I.

The initial blood sugar value was within normal limits, but at the time sugar was being excreted by the kidneys at the rate of 2.98 grams per hour.

The blood sugar curve reached its highest point in one hour and returned to its original value in two and a half hours, as is normally the case. The rate of sugar excretion increased with the blood sugar, so that when the latter was at a concentration of 0.189 per cent., sugar was being excreted at the enormous rate of 9.9 grams per hour. (A comparison of the rate of fluid excretion with the concentration of sugar in the blood is interesting, as during the rapidly developing hyperglycemia the fluid excretion dropped off markedly and then quickly increased as the kidneys rapidly removed the excess of sugar from the blood. This decreased excretion occurred in spite of the fact that 400 c.c. of fluid were imbibed with the glucose.)

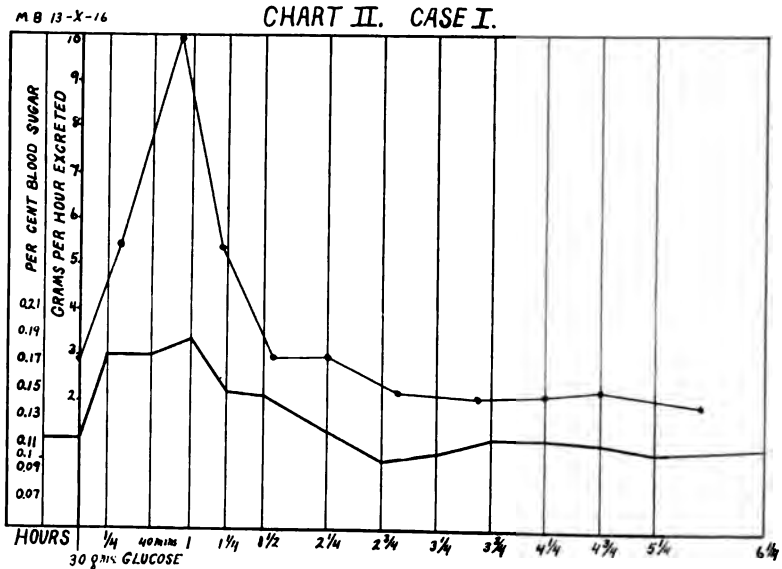
If we compare the findings at this time with those of the similar test taken fourteen months previous (at which time the patient was four months pregnant) we notice that the blood sugar in the fasting state has increased to the normal value. This, however, is easily explained, as the tests in August, 1915, were made following three days of fasting, while the latter tests followed but a ten-hour fast. The excretory power of the kidneys for glucose has increased, and the more rapid rise of blood sugar following the ingestion of glucose probably indicates an increase in absorptive power of the intestines.

The general condition of the patient was unchanged. Her chief complaint was lack of reserve energy. This was most distressing upon restricting the diet. The urine sugar remained above 6 per cent. in the twenty-four-hour specimens.

The patient was again examined on December 20, 1917. Her physical condition remained unchanged. She stated that for the preceding fourteen months her health had been excellent, her only complaint being lack of reserve energy. Her diet was unrestricted. Examination of a twenty-four-hour urine specimen on November 4, 1918, showed an excretion of 1440 c.c.; specific gravity 1040; sugar 4.5 per cent.; albumin negative.

TABLE IV.—CASE I.  
M. B., October 13, 1916.

Time.		Blood.		Urine.			Fluid intake. c.c.
A.M.		Hemo- globin. Units.	Sugar. Per cent.	c.c. per hour.	Sugar.		
					Per cent.	Grams per hour.	
9.15	....	67	0.116	63.0	8.3	2.98	400
9.30	....	30 grams glucose.					
9.45	$\frac{1}{2}$ hr.	62	0.177	.....	.....	.....	
10.10	$\frac{1}{2}$ hr.	61	0.177	36.0	11.9	5.35	
10.30	1 hr.	62	0.189				
10.40	.....	.....		45.0	3.0	9.90	
10.50	$1\frac{1}{2}$ hrs.	63	0.150				
11.00	.....	.....		33.0	1.6	5.28	
11.10	$1\frac{1}{2}$ hrs.	64	0.147				
11.30	.....	.....		80.0	3.7	2.96	
11.45	$2\frac{1}{2}$ hrs.	65	0.120	120.0	2.5	3.00	
12 M.	.....	.....					
12.15	$2\frac{1}{2}$ hrs.	65	0.100	37.0	6.2	2.31	
12.45	$3\frac{1}{2}$ hrs.	66	0.106				
1.15	$3\frac{1}{2}$ hrs.	67	0.116				
1.30	.....	.....		56.0	5.6	2.09	
1.45	$4\frac{1}{2}$ hrs.	67	0.114				
2 P.M.	.....	.....		36.0	6.0	2.16	
2.15	$4\frac{1}{2}$ hrs.	67	0.112				
2.30	.....	.....		34.0	6.5	2.21	
2.45	$5\frac{1}{2}$ hrs.	68	0.106				
3.30	.....	.....		28.0	6.8	1.90	
3.45	$6\frac{1}{2}$ hrs.	68	0.108				



SUMMARY. The case reported is one of constant glycosuria without hyperglycemia. Alimentary hyperglycemia while the patient

was pregnant was slightly delayed and prolonged, this being probably due to decreased functional activity of the bowels and kidneys. Alimentary hyperglycemia in the non-pregnant state was of the normal type,<sup>18</sup> the curve reaching its highest point in about one hour, returning to the original value in two and a half hours, falling to a lower point in three hours, then increasing and maintaining its level in three and a half to four hours' time. Alimentary glycosuria was excessive. It varied directly with the glycemia and was present to a marked degree even in the presence of a hypoglycemia, the permeable point of the kidneys being below a blood sugar concentration of 0.086 per cent. (the normal kidneys being permeable between 0.16 and 0.17 per cent.). The patient's history points strongly to this being a congenital condition.

Since the accidental discovery of sugar in her urine in 1908 her condition has remained unchanged, although her diet has never been restricted. Her daily output of sugar is about 20 grams.

CASE II.—J. E. P., English-American, aged sixty-two years, a toolmaker by trade, was admitted to the New York Post-Graduate Hospital, to the service of Dr. Quintard, on August 25, 1915. Case History No. 5940. He complained of swelling of the feet and abdomen and shortness of breath.

*Family History.* Mother died at seventy-six, cause unknown; father died at thirty-nine, cause unknown. Three brothers and three sisters are alive and well. No history of obesity, diabetes, nephritis, gout, goitre, tuberculosis, rheumatism or heart disease.

*Personal History.* Born in England of English parentage. Came to the United States when a young man. With the exception of a gall-bladder disturbance, for which he was operated upon thirteen years ago, he has enjoyed good health up to the onset of his present illness. He has no knowledge of disease in childhood and denies having had venereal disease. He was married twice; the first wife bore eleven healthy children and no miscarriages; the second wife is alive and in good health.

*Habits.* Alcohol in moderation. For years he has used tobacco to excess and has been a heavy meat-eater. He has never engaged in dangerous occupations.

*History of Present Illness.* Dates back two years, when he noticed dizziness, spots before the eyes, failing vision and severe headaches. Six months later he noticed a puffiness under the eyes and swelling of the feet and legs. These symptoms gradually increased in severity and three months ago he developed dyspnea on slight exertion, and the necessity of urinating at least once at night. Shortly before coming to the hospital he became very restless and orthopneic. His appetite has always been good, never ravenous; bowels regular; never jaundiced; no blood in stools; no nausea or vomiting; no gastric disturbances, cough or hemoptysis. His daily output of urine has not been increased. He has had none of the symptoms

associated with diabetes (polyphagia, polydypsia, polyuria, obesity, emaciation, skin lesions, pruritus or neuritides); no symptoms of disturbance of the hypophysis, thyroid, pancreas or adrenals. He has no knowledge of having passed sugar in his urine.

*Physical Examination.* Well-developed and well-nourished male. Height 5 feet 6 inches; weight 198½ pounds, lying in dorsal position moderately dyspneic; marked generalized edema, especially of feet, legs, thighs, scrotum and hands; abdomen pendulous and edematous; slight cyanosis of ears, nose and lips; skin dry, scaly and transparent; soft edema about eyes; sclera clear, pupils equal, regular in outline and react well to light and accommodation; von Graefe's sign absent; no exophthalmos; no widening of palpable fissure; tongue coated; teeth decayed; marked pyorrhea; nothing abnormal found in nose or throat; veins of the neck engorged; thyroid palpable but not enlarged or pulsating; thorax emphysematous and symmetrical; expansion poor; respirations shallow; moist rales heard over base of lungs and free fluid can be demonstrated in the pleural cavities; temperature 98°; pulse 84; respirations 22; pulse irregular and unequal; arteries hypertrophied; apex beat diffuse and heaving; no thrill over precordium; area of cardiac dullness 3 cm. to right and 12 cm. to left of midsternal line; aortic second sound accentuated; no adventitious sounds; blood-pressure: systolic 190; diastolic 130; marked edema of abdominal walls; old scar in region of gall-bladder; moderate ascites; a small indirect inguinal hernia on right side just emerges from the external ring but does not descend into the scrotum; on the left side is a small hernia just reaching the external ring; scrotum very edematous and the tunica vaginalis on the right side distended with fluid; liver, kidneys and spleen not palpable; reflexes (abdominal cremasteric, knee-jerk, ankle-jerk, etc.) all present and active; no ataxia; Rhomberg negative; skin shows a dark brown pigmentation over the lower chest and the upper abdomen; dry, scaly eczema over both tibiae.

The fundus of the right eye shows an angiopathic neuroretinitis, with numerous areas of fatty degeneration in macular region and numerous flame-shaped hemorrhages along the vessels near the disks. The left eye shows a cloudy vitreous with large floating bodies occluding the view of the fundus.

Volume of twenty-four-hour specimen of urine 625 c.c.; color dark amber; specific gravity 1025; dry protein per liter 3.1 grams; sugar 0.6 per cent.; total chlorines as NaCl 6.6. grams; acetone negative; diacetic acid negative; many hyaline and granular casts; phenolsulphonephthalein excreted 8 per cent. in two hours.

An examination of the blood shows 83 per cent. hemoglobin; 4,592,000 erythrocytes; 12,400 leukocytes, of which 74 per cent. are polymorphonuclears and 23 per cent. lymphocytes.

Complement-fixation test for syphilis negative. Chemical blood analysis during fasting showed blood sugar 0.18 per cent.; chlorides

as NaCl 0.73 per cent.; urea nitrogen 23 mg. per 100 c.c. blood; uric acid 4.0 mg. per 100 c.c. blood; creatin 7.4 mg. per 100 c.c. blood; creatinin 1.9 mg. per 100 c.c. blood.

*Subsequent History.* The patient remained in the hospital ten months and underwent ordinary treatment for chronic parenchymatous nephritis. At times he showed marked improvement, followed by relapses, and finally died on June 1, 1916. During his stay in the hospital his urine was never free from sugar, the percentage remaining in the neighborhood of 0.5 per cent., varying slightly inversely with the volume and seemingly independent of the diet.

*Test of Alimentary Hyperglycemia and Glycosuria.* On the morning of December 13, 1915, before the patient had anything to eat or drink, specimens of his blood and urine were obtained. He was then given 33 grams glucose in 250 c.c. of weak tea, and specimens of blood and urine were obtained as frequently as possible for the succeeding five and a quarter hours. The findings are recorded in Table V, Case II, and Chart I, Case II.

It will be noticed that the initial blood sugar value is that commonly met with in cases of severe nephritis.<sup>21</sup> The urine, however, contained 0.52 per cent. glucose, the excretion being at the rate of 0.22 gram per hour. Alimentary hyperglycemia was delayed, reaching its maximum in one and a half hours and not returning to normal until four and a quarter hours had elapsed. The rate of urinary excretion decreased and was uninfluenced by the fluid intake. The rate of sugar excretion varied directly with the excretion of urine and bore no relation to the concentration of sugar in the blood. The blood volume, as indicated by the hemoglobin, showed a slight increase at the onset of the hyperglycemia, but returned to the original value in one and a half hours.

On March 11, 1916, the test was repeated, using on this occasion 75 grams glucose in 450 c.c. of weak tea. The general condition of the patient was the same as at the time of the previous test. The results are shown in Table II and Chart II, Case II.

One sees that in this second test the alimentary hyperglycemia was delayed and prolonged. The greatest concentration occurred at the end of two hours while his normal value had not been reached at the end of six and a quarter hours.

The rate of urinary excretion decreased during the development of the hyperglycemia and was practically uninfluenced by the fluid intake. The rate of sugar excretion again fell rapidly with the development of the hyperglycemia and had not begun to increase by the end of the test.

If one were to judge this case by a consideration of the concentration of sugar in the urine it would seem that we had a patient who excreted urine containing about 0.5 per cent. glucose and that this was independent of the blood sugar up to the latter's concen-

<sup>21</sup> C. V. Bailey: Proc. Soc. Exper. Biol. and Med., 1916, xiii, 153.

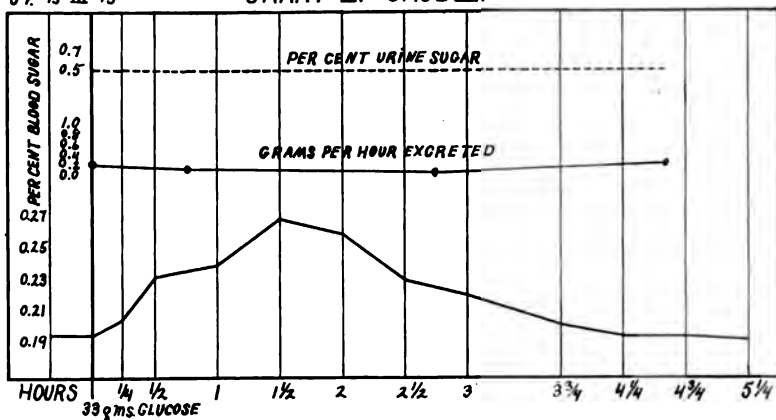
tration of about 0.26 per cent. At this point the kidneys became intolerant and more sugar appeared in the urine.

TABLE V.—CASE II.  
J. E. P., December 13, 1915.

A. M.	Time.	Blood.		c.c. per hour.	Urine.			Fluid intake. c.c.
		Hemo-globin. Units.	Sugar. Per cent.		Sugar.		Chlorides, grams per hour.	
					Per cent.	Grams per hour.	Specific gravity.	
9.25	....	67.5	0.196	42	0.52	0.220	1015	250
9.30		33 grams glucose.						
9.45	1 hr.	64.0	0.208					
10.00	1 hr.	65.0	0.234					
10.30	1 hr.	65.5	0.240	36	0.51	0.186	1015	250
11.00	1 1/4 hrs.	67.5	0.270					
11.30	2 hrs.	67.0	0.260					
12 M.	2 1/4 hrs.	68.0	0.232					
12.30	3 hrs.	67.5	0.224	33	0.51	0.170	1016	0.142
1.15	3 1/4 hrs.	67.5	0.204					
1.30								
1.45	4 1/4 hrs.	67.5	0.196					
2.15	4 1/4 hrs.	68.0	0.196	42	0.52	0.210	1013	0.190
2.45	5 1/4 hrs.	67.5	0.192					

J. P. 13-III-15

CHART I. CASE II.

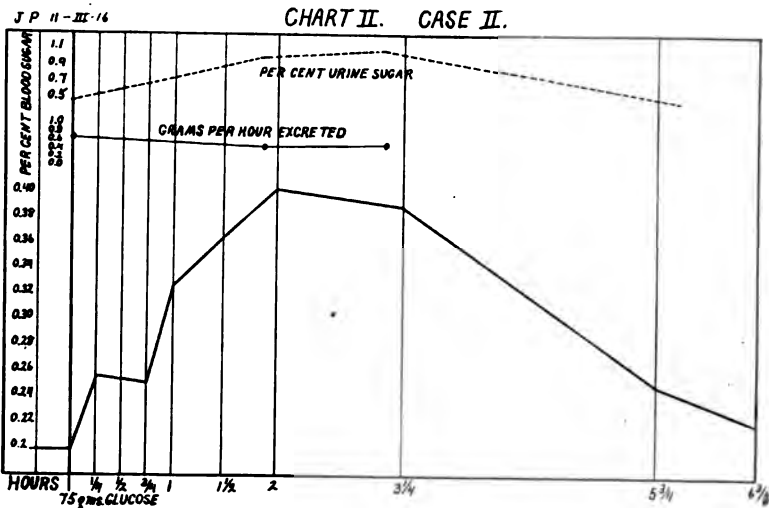


However, we see that the reverse is the case when we consider the actual excretory work done by the kidneys, the glucose being expressed in grams per hour. In Table I the kidneys excreted 0.22 gram of glucose per hour when the blood sugar was 0.196 per cent.; as the blood sugar increased the excretion of sugar decreased, so that when the blood contained 0.24 per cent. the sugar excretion had dropped to 0.17 gram per hour. The rate of excretion increased to 0.216 gram per hour when the blood sugar returned to the original

value, 0.196 per cent. In Table VI, Case II, Chart II, Case II, the same observations can be made.

TABLE VI.—CASE II.  
J. E. P., March 11, 1916.

Time.		Blood.		Urine.				Fluid intake. c.c.
A.M.		Hemo- globin. Units.	Sugar. Per cent.	c.c. per hour.	Specific gravity.	Sugar.		
						Per cent.	Grams per hour.	
9.20	....	65.0	0.20	144	1015	0.5	0.72	450
9.30		75 grams glucose.		...	....	...	....	
9.45	1 hr.	65.0	0.258					
10.05	2 hr.	65.0	0.256					
10.20	3 hr.	64.0	0.252	52	1013	1.0	0.52	250
10.35	1 hr.	64.0	0.329					
11.00	1 1/2 hrs.	63.5	0.368	...	....	...	....	
11.20								
11.30	2 hrs.	63.5	0.405					500
12.45	3 1/2 hrs.	64.0	0.390	56	1015	1.1	0.61	
1.30								
3.15	5 1/2 hrs.	65.0	0.250					
4.15	6 1/2 hrs.	65.0	0.220	?	1014	0.5	?	
7.35								



*Summary.* The case reported gave the subjective and objective symptoms of chronic parenchymatous nephritis. Nothing in the patient's history or in the physical finding would lead one to suspect a disorder of carbohydrate metabolism. He had a constant hyperglycemia, but no higher than is ordinarily found in chronic nephritis. The blood sugar curve following the ingestion of glucose was of the

type found in non-diabetic nephritis. Of special interest is the fact that glucose constantly appeared in his urine and that the rate of excretion was greatest when the blood sugar concentration was low. A hyperglycemia was accompanied by a decreased excretion of sugar.

**CONCLUSIONS.** Renal diabetes, or better "renal glycuressis,"<sup>22</sup> should be broadly considered as a condition of glycuressis not dependent upon a temporary increase of blood sugar in an individual free from symptoms of diabetes mellitus.

The condition can be recognized by morning synchronous blood and urine sugar tests, the specimens being collected before the patient has had anything to eat or drink.

At least two types can be recognized: (1) Cases with normal or subnormal blood sugar and glycuressis, which is greatly influenced by blood sugar changes; (2) cases with a constant glycuressis which varies with the rate of urinary excretion and is little influenced by blood sugar changes. The possibility of renal glycuressis being in some cases a congenital condition; the question whether or not the clinical course remains permanently free from symptoms of diabetes mellitus; the lack of reserve energy which such a condition produces, if severe; the direct effect upon the kidney of continued excretion of sugar are interesting points to be observed in this condition.

I wish to thank Professor Edward Quintard, director of the department of medicine, and Professor Victor C. Myers, director of the laboratory of pathological chemistry, for helping me in this work.

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## MULTIPLE ENDOTHELIOMA OF THE SKIN.

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**CONCEPTION OF ENDOTHELIOMA AS AN ENTITY.** Dermatological literature records many instances of single and multiple tumors which clinically were thought to be various types of nevi or sarcoma or syringocystadenoma, and which, after microscopic study, were identified as endothelioma by some and as epithelioma or carcinoma by others. Gottheil,<sup>1</sup> for example, published the report of a case of a pigmented tumor of the foot which clinically was considered to be a pigmented sarcoma or melanoma, but on section proved to be an

<sup>22</sup> Benedict, S. R., and Osterberg, E.: Jour. Biol. Chem., 1918, xxxiv, 258.

<sup>1</sup> Endothelioma of the Skin, Jour. Am. Med. Assn., January 12, 1907, xlviii, p. 93.



endothelioma. Juliusberg<sup>2</sup> reported a tumor of the abdomen, the histological structure of which induced him to classify the growth with the endothelioma group. His microscopic interpretation was severely criticized by a number of competent pathologists, such as Krompecher,<sup>3</sup> Ribbert,<sup>4</sup> Hoffmann,<sup>5</sup> Fick<sup>6</sup> and Friboes.<sup>7</sup> These authorities believed that with one or two rare exceptions all the so-called endotheliomas are in reality benign types of basal-cell epitheliomas or carcinomas. Fick somewhat vehemently asserted that the entire conception of endothelioma was an erroneous one, based on false interpretations of the histological pictures, and that an endothelioma never saw the light of day. His contention was that the so-called endothelial cells are actually epithelial cells, derived probably from the glandular structures of the skin. In a paper which he published under the title of "The Impracticability of 'Endothelioma' as a Working Hypothesis" (which I abstracted in the *Journal of Cutaneous Diseases* several years ago),<sup>8</sup> Fick not only criticizes all those writers who had the temerity to regard a growth as being an endothelioma, but severely arraigns those who permitted themselves to believe that such a conception is within the bounds of possibility.

In 1902 Borst<sup>9</sup> undertook the task of analyzing the microscopic findings of most of the tumors said to be of endothelial origin, and came to the conclusion that some of them undoubtedly deserved the title of endothelioma. In the following year his views were strongly opposed by Krompecher,<sup>10</sup> who contended that all of the so-called endotheliomas were epitheliomas or carcinomas, having their origin either from the basal-cell layer of the superficial epithelium of the follicles or of the glandular epithelium, and the cellular elements of which corresponded in every way with those of the basal cells. He therefore called them basal-cell epitheliomas, and his opinions, as before mentioned, were accepted by a large number of investigators. Zeit,<sup>11</sup> in 1906, published a very instructive article on the subject, in which he maintained that certain forms of sarcoma and carcinoma were in reality examples of endothelioma. Zeit's views are seldom

<sup>2</sup> Lymphangio-endothelioma Cutis Abdominis, Arch. f. Dermat. u. Syph., 1908, lxxxix, p. 77.

<sup>3</sup> Zur Histogenese und Morphologie der Mischgeschwülste, Ziegler's Beitr., 1908, xliv, p. 51. Ueber die Beziehungen zwischen Epithel und Bindegewebe, Ziegler's Beitr., 1908, xlv, p. 131.

<sup>4</sup> Das Karzinom des Menschen, Bonn, 1911.

<sup>5</sup> Case Demonstration, Deutsch. med. Wchnschr., 1910, I, p. 2365.

<sup>6</sup> Ueber die Endotheliome der Haut, Monatsh. f. prakt. Dermat., 1909, xlviii, p. 199. Ueber die Unbrauchbarkeit der Arbeitshypothese "Endotheliome," Dermat. Wchnschr., 1912, liv, p. 488.

<sup>7</sup> Beitrag zur Klinik und Histopathologie der gutartigen Hauteptitheliome, S. Karger, Berlin, 1912.

<sup>8</sup> Jour. Cutan. Dis., 1912, p. 444.

<sup>9</sup> Die Geschwülste, 1902.

<sup>10</sup> Das Basalzellenkrebs, Fischer, Jena, 1903.

<sup>11</sup> Endothelioma, Jour. Am. Med. Assn., 1906, xlv, p. 567.

if ever mentioned in the foreign literature, but they receive a well-earned recognition in Hazen's<sup>12</sup> book on *Skin Cancer*. Hazen classifies the endotheliomas under three heads: lymphangio-endothelioma, hemangio-endothelioma and perithelioma. With regard to the last, Hazen says: "The perithelial tumors originate from the endothelium lining the perivascular lymph spaces, and hence there is some discussion as to whether they should be called hemangio-endotheliomas or lymphangio-endotheliomas, according to some authors. On the other hand, Zeit emphatically says: 'The perithelial membrane must be differentiated from the perivascular lymph spaces of His, which he found surrounding the adventitia of arteries, veins and capillaries of the central nervous system. The perithelium is the outer lining of the adventitia of bloodvessels, outside of which is the perivascular lymph space.' Zeit further states that the true peritheliomata are the tumors arising from the perithelium and not from the lymph space, and hence should be called hemangio-endothelioma perivascular. At any rate, up to the present time there is in the literature but one definite case report of a perithelioma of the skin, and that is a case reported by Brandeis and Pouget,<sup>13</sup> in which there were a number of metastases from a tumor of the adrenals." Hazen then devotes several paragraphs to Zeit's conception of the histological differences between endothelioma and carcinoma.

A compilation of 25 cases of tumors which had been designated as lymphangio-endotheliomas was made by Friboes in 1912. Of these, 3 examples were under his own observation, and his monograph includes a complete study of these as well as of nearly all other cases recorded in the literature. (The cases of Gottheil,<sup>1</sup> Allen<sup>14</sup> and Hartzell<sup>15</sup> are not included). Most of these growths were described as multiple tumors of the scalp and trunk. Many of them corresponded to the peculiar turban-like tumors of the scalp, described by Spiegler,<sup>16</sup> with which most readers are familiar, chiefly on account of the striking illustration of one of Spiegler's cases, seen in most of the older text-books. Of these 25 cases, 19 were in women and 6 in men. In 23, the tumors were multiple and single in 2. Their sites were: the hairy scalp only, in 10, the hairy scalp and the face in 1, the scalp and trunk in 9, the scalp, trunk and extremities in 5. The tumors appeared usually between the second and fourth decades. They varied in size from a pinhead to an orange; the small ones were usually rounded and sometimes lobulated; the larger ones were hemispherical, distinctly lobulated, with rounded, prominently bulging masses, the outline of the mass, as a whole, being

<sup>12</sup> Hazen: *Skin Cancer*, Mosby, St. Louis, 1916, p. 127.

<sup>13</sup> *Ann. d. dermat. et de syph.*, 1910, 5th S., i, p. 506.

<sup>14</sup> *Monatsh. f. prakt. Dermat.*, 1900, xxxi, p. 47.

<sup>15</sup> *British Jour. Dermat.*, October, 1904. *Diseases of the Skin*, Philadelphia.

<sup>16</sup> *Ueber Endotheliome der Haut*, *Arch. f. Dermat. u. Syph.*, 1899, i, p. 163.

aptly compared to that of a tomato. They were situated partly within and partly beneath the skin, resting on a broad sessile base. The masses were easily movable, but the skin covering them was usually quite adherent, especially over their central portions. Most of the tumors presented dilated bloodvessels in the skin which enveloped them. The closely set tumors were separated by deep grooves, within which the hair was still present, while their surfaces were entirely devoid of hair, excepting in the smallest tumors. The color of the more prominent masses was rose red, yellowish red, dark red or livid, with many tinctorial transitions. The skin covering the smaller tumors was usually normal in color. Small erosions of the surface of some of the larger tumors sometimes occurred as a result of the accumulation of dirt, sweat and sebaceous material, giving rise to irritation. Breaking down of the tumors occurred in 3 instances (Haslund,<sup>17</sup> de Beurmann<sup>18</sup> and Friboes<sup>19</sup>). Metastases took place in 2 (Ansell<sup>20</sup> and Haslund). Autopsies were performed in five of the patients (Ansell, Riehl,<sup>21</sup> de Beurmann, Friboes and Leeuwen).<sup>22</sup> In Ansell's patient there were severe visceral metastases, in the other four no signs of metastases were discoverable. Recurrences of the growth *in loco*, after extirpation, occurred only in Ansell's case.

Summing up his conclusions, based on a thorough analysis of these 25 cases, Friboes states his belief that with very few exceptions they represented examples of very slowly developing, peculiar types of benign epitheliomas.

In his recently published text-book Hartzell<sup>23</sup> summarizes the subject of cutaneous endothelioma in these words:

"The nature of the neoplasm is still a matter of some uncertainty. As already noted the earlier cases were regarded as a form of sarcoma, but this view is no longer entertained. In its prolonged and benign course and in its histopathology it is quite unlike any of the varieties of that neoplasm. Most recent authors agree with Spiegler in classifying it as an endothelioma. Quite recently, however, Dubreuilh and Auché, who have studied its histopathology with great care and detail, expressed the opinion that it is a variety of multiple benign epithelioma, having its origin in the epidermis and perhaps the hair follicles, and resembling much, in the character of the cells which compose it, rodent ulcer.

"According to Spiegler the tumor is composed of branching and

<sup>17</sup> Multiple Endotheliome der Kopfhaut, Arch. f. Dermat. u. Syph., 1906, 82.

<sup>18</sup> Cylindrome de la face et du cuir chevelu, Ann. d. dermat. et d. syph., 1911, p. 577.

<sup>19</sup> Loc. cit.

<sup>20</sup> Quoted by Friboes (loc. cit.).

<sup>21</sup> Endotheliom der Haut, Monatsh. f. prakt. Dermat., 1894, xix, p. 434.

<sup>22</sup> Multiple Epitheliome der Haut mit Mischgeschwulst der Parotis, Virchows Arch., 1912, ccvii, p. 330.

<sup>23</sup> Loc. cit.

intersecting cylindrical tracts of cells resembling small epithelial cells occupying the derma. About the margin of these tracts, which are surrounded by a fine fibrous capsule and contain numerous small round and oval masses of hyaline material, the cells are of the columnar type and are arranged radially, while those in the interior are round or polygonal."

**SOFT NEVI.** Before taking up the description of the cases which form the subject of this paper, I should like to revert to certain anomalies or pathological changes in the skin which are of interest, both from the clinical and histological standpoint, in connection with cutaneous endothelial growths. The first of these are the soft nevi. Demieville,<sup>24</sup> in 1880, was the first to attract attention to the so-called nevus cells occurring in groups, strands and isolated areas within the corium. These were thought by him to be derived from the endothelial cells of the blood capillaries, and the nevi were looked upon as being endothelial tumors. Von Recklinghausen,<sup>25</sup> in 1882, stated his belief that the nevus cells had their origin in the endothelial cells lining the lymph spaces. His theory was that nevus cells, derived from the endothelial cells of some of the vessels, would develop in a certain area of the integument, through the growth of individual cellular elements which proliferated and were transformed into so-called nevus cells. Unna,<sup>26</sup> in 1893, opposed the view that these specialized cells were of endothelial origin and offered a number of reasons for considering them to be of epithelial origin. He based his opinions on the microscopic examination of a considerable number of soft nevi occurring in the newborn and stated (in his *Histopathology*, 1894) that the epithelial derivation of the nevus cells was demonstrable with much greater facility in preparations of nevi from the newborn as compared with those studied from the adult. Many subsequent writers, such as Delbanco, Kromayer, Gilchrist, Ravogli, Whitfield and Krompecher,<sup>27</sup> have since subscribed to Unna's views, so that by many it has become an accepted dictum that the derivation of nevus cells from the epithelial elements has been satisfactorily demonstrated in a number of instances, more especially in the soft nevi of the newborn, but also in isolated adult preparations.

**SYRINGOCYSTADENOMA.** The second type of lesion deserving mention in this connection is syringocystadenoma. Here, however, the interest lies chiefly in the clinical features which characterize this condition. Of the two cases of endothelioma which form the subject of this report, one presented a clinical picture which was almost identical with that of syringocystadenoma as it appears on the trunk. With regard to its histopathological features, an over-

<sup>24</sup> Quoted by Unna, *Histopathologie*, 1894.

<sup>25</sup> Quoted by Fick: *Monatsh. f. prakt. Dermat.*, 1909, xlviii, p. 199.

<sup>26</sup> *Histopathologie der Haut*, 1894.

<sup>27</sup> Quoted by Fick: *Monatsh. f. prakt. Dermat.*, 1909, xlviii, p. 205.

whelming majority of investigators have shown that the canals and cellular strands and the lining of the cysts are of epithelial origin, not endothelial. In some cases it has been successfully demonstrated that there is no breach of continuity between the lining of the cyst walls and the excretory ducts of the sweat glands. The epithelial derivation of these tumors is recognized by Darier and Jacquet, Unna, Jadassohn, Fordyce, White, Sutton, Hartzell, Heidingsfeld<sup>28</sup> and many others.

NEVO-XANTHO-ENDOTHELIOMA. Lastly, I must devote a few words to a type of new growth which McDonagh<sup>29</sup> aptly named nevo-xantho-endothelioma. In the second case of endothelioma, which will be described further on, I made the erroneous clinical diagnosis of urticaria pigmentosa or xanthelasmoidea, a diagnosis with which many of my colleagues concurred without hesitation. Microscopic examination demonstrated the fact that the tumors consisted of cells of endothelial origin. McDonagh described several cases which can be classed in this group, most of them having been diagnosed as urticaria pigmentosa, xanthelasmoidea, multiple angiomas, etc., until microscopic examination revealed them to be new growths of endothelial origin.

#### REPORT OF CASES.

CASE I (see Figs. 1 and 2).—*Endothelioma Simplex*. Abner W., male, aged thirty-two years, a native of this country, was unmarried and a clerk by occupation. He applied at the dermatological dispensary of Mt. Sinai Hospital for the removal of numerous "moles" on various parts of the body. He stated that these little growths first made their appearance in early childhood and had been few and widely scattered until about ten years ago, when his attention was attracted to several scores of new lesions on the chest and back. His account of the trouble was quite vague and unreliable, as he always had considered the blemishes as a trivial matter and paid very little attention to them. More recently, many comedones and acne papules and pustules had appeared on the chest, mingling with the older tumor-like growths in this locality.

*History.* The father died of endocarditis; the patient said that many "similar blemishes" had been present on his father's back and chest, but he did not know at what age they had appeared; as far as he knew they never gave his father cause for complaint. Two brothers of the patient had several "moles" on the chest and back, but whether or not they resembled his own, he was unable to say.

<sup>28</sup> Quoted by Hazen: *Skin Cancer*, p. 102.

<sup>29</sup> Nevo-xantho-endothelioma, *British Jour. Dermat.*, 1912, xxiv, p. 85. Also, *Biology and Treatment of Venereal Diseases and the Biology of Inflammation and its Relationship to Malignant Disease*, London, 1915.

His mother and two sisters were free of cutaneous disorders or blemishes.

*Physical Examination.* The patient was well built and in good health. Physical examination was negative, save for disease of one ear, said to have resulted from a fall on the head in infancy, and causing deafness.



FIG. 1.—Case I. Multiple endothelial tumors of the skin. Comedones and acne over the sternum. The crusted lesions on the left side are sites of biopsies.

*Description of Eruption.* Between 125 and 150 papular lesions were scattered on various parts of the body. They were most abundant on the chest and back, more widely scattered on the arms, thighs and the neck. The face and scalp, forearms, legs, hands and feet were free.

The lesions consisted of well-formed papular elements, ranging in size from a pinhead to a lentil. They were soft and elastic. They varied in color: some were rose red, some brown, some salmon yellow, while a few, situated over the sternum, had the color of normal skin,

so that they were more readily felt than seen. Most of the little tumors were round or oval, projecting from a sixteenth to an eighth of an inch above the surrounding skin. The great majority of the tumors consisted of single well-defined and distinct papules; others, however, appeared to have formed as the result of the coalescence of two or even three individual growths, producing a lobulated or segmented structure. The skin covering the tumors was soft,



FIG. 2.—Case I. Side view of the same patient.

velvety and wrinkled in the larger and older lesions and smooth and somewhat stretched over the smaller and younger ones. There were several flat, pea-sized growths on the inner and upper surfaces of the thighs, rather firm to the touch as compared with the others, and bearing a striking resemblance to xanthomata. None of the growths had ever broken down or ulcerated.

At the lower portion of the sternum were many large comedones and acne papules and pustules. (The crusted lesions on the left side of the chest, seen in the photograph, are the sites of biopsies.)

Subjective symptoms were absent, the patient desiring removal of the blemishes for cosmetic reasons alone.<sup>30</sup>

CASE II (see Fig. 3).—*Nevo-xantho-endothelioma*. Abraham W., male, aged twenty-two months, born in this country of Russian Jewish parentage, applied for treatment in the dermatological department of the Vanderbilt Clinic, January 6, 1917. The child's family history and personal history were negative.

*Physical examination* revealed a healthy, strapping infant, presenting a well-marked macular and papular eruption on the trunk and extremities, most abundant on the abdomen.

*Description of Eruption*. The eruption consisted of many hundreds of lentil to pea-sized macules and papules, the latter predominating. The macules were rose red and bluish red in color, faintly convex, round and oval in outline; the papules were more pronounced in color, most of them being yellowish brown and salmon yellow in tint; they averaged about the size of a split pea and were most prominent on the abdomen, gradually giving place to flat papular and barely raised macular lesions on the chest and extremities; the back and the buttocks also were studded with well-defined papules. There were no urticarial wheals nor evidences of pruritus, although the mother stated that the eruption was preceded by a rash resembling mosquito bites. The disease first manifested itself when the infant was about a year old. No fresh lesions had recently appeared. The face, scalp, neck, hands and feet were free. There were no signs of dermatographism. Pressure on the lesions with a piece of glass did not result in a lessening of their color to any appreciable extent.

The eruption was labelled urticaria pigmentosa or xanthelasma-moidea. The child was again observed about six months later and the eruption had remained unaltered.

CLINICAL DIFFERENTIATION. The eruption in Case I closely simulated two cutaneous anomalies: ordinary soft, pigmented moles or nevi, and syringocystadenoma. Taking an individual lesion for a criterion of clinical diagnosis it would be impossible to differentiate it from an ordinary soft mole; but on considering the multiplicity of the tumors, their unusually widespread dissemination, the variations in color and surface markings, the lobulated formation of some of them, the problem of arriving at a clinical diagnosis remained unsettled. The resemblance to syringocystadenoma was less suggestive; still, that condition called for careful consideration: the history of the eruption, the distribution and size of the lesions, their insidious appearance, the absence of subjective sensations and various other factors, such as the occurrence in several members of the family, justified at least a serious consideration of the alter-

<sup>30</sup> The blemishes were removed by applications of trichloroacetic acid. There has been no recurrence in a year.



native diagnosis. In syringocystadenoma, however, the little tumors are rarely if ever so deeply tinted (except when they occur in the negro, of which I have seen two examples); the tumors are not so sharply defined; their peripheries slope and the individual papules are frequently bordered by a narrow band of erythematous or pigmented skin; the endothelial tumors, on the other hand, were quite sharply demarcated, with abrupt peripheries; the elements of syringocystadenoma give the impression of being *in* the skin, while the endotheliomata in this patient readily impressed the observer as being *on* the skin.

With regard to the second patient, the infant, little more can be said except that the clinical diagnosis of urticaria pigmentosa was concurred in by a dozen competent dermatologists. Not until the microscope revealed the true state of affairs did anyone entertain the slightest suspicion that the eruption was composed of formations resulting from endothelial cellular proliferation.

As stated, McDonagh christened this dermatosis nevo-xantho-endothelioma. To those who are uninitiated in the complexities and niceties (?) of dermatological nomenclature the prefix, nevo-xantho may be a source of confusion. A nevus is a blemish which may be present at birth, may appear early in infancy and sometimes even in late adult life. "Xantho" refers, of course, to the yellow tint of the lesions. Now it so happens that urticaria pigmentosa is also known under the name of xanthelasmoidea, on account of the close similarity, clinically, to the little tumors of xanthoma. Some eruptions of urticaria pigmentosa simulate xanthomata to such an extent that only a microscopic examination can tell them apart. McDonagh calls attention to the erroneous diagnosis of urticaria pigmentosa or xanthelasmoidea applied to eruptions which proved (as in Case II), on microscopic examination, to be endotheliomata, appearing at birth or early in infancy. Hence the name, nevo-xantho-endothelioma.

In this connection attention should be called to the fact that the lesions in Case I also would by many pathologists be regarded in the light of nevi of endothelial origin. From the pathologist's point of view a nevus may make its appearance at any period in life; the pathologist's conception of the term embraces a far more comprehensive group of cutaneous anomalies than does that of the clinician; for example, ichthyosis, xeroderma pigmentosum, syringocystadenoma, benign cystic epithelioma, lymphangioma circumscriptum and several other morbid changes in the skin are by many considered to belong in the nevus group. This question, as already intimated, is still undecided. The whole subject is, I think, very interestingly discussed by McDonagh, in his chapter on "The Role Played by the Endothelial Cell in Inflammation and its Probable Relationship to Sarcoma." Most dermatologists will find this to be a rather refreshing bit of reading, and certainly well worth the while.

**HISTOPATHOLOGY** (see Figs. 3, 4, 5, 6, 7, 8, 9). Three tumors of different sizes and seemingly various ages were removed from Case I and one papule from Case II for purposes of microscopic study. These were sectioned and stained with hematoxylin-eosin, van Gieson, polychrome methylene blue, Unna-Pappenheim, acid-orcein and Weigert's elastic-tissue stains.



FIG. 3.—Case II. Endothelioma cutis. The eruption closely resembles urticaria pigmentosa.

The only noteworthy difference between the microscopic structures of the young and older lesions consisted in a correspondingly lesser or greater amount of cellular infiltration in the corium and in unimportant secondary changes in the epidermis, due to pressure exerted upon it by the underlying infiltrate. When the subepidermal infiltrate was sparse the epidermal layer was practically unaltered; when the infiltrate was abundant the covering epithelium was flattened and compressed. The sections here described were cut from a young lesion, and from another, apparently fully developed old lesion, taken from Case I, and from a fully developed pea-sized papule, taken from Case II.

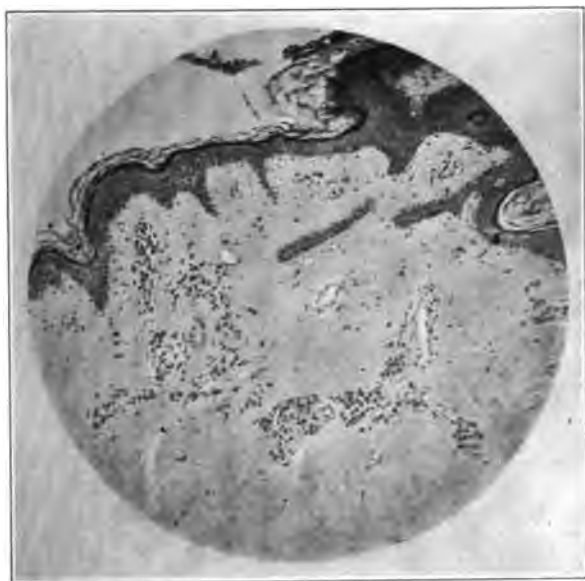


FIG. 4.—Case I. Endothelioma, early lesion showing derivation of cells.



FIG. 5.—Case I. Endothelioma, early lesion showing derivation of cells.

His mother and two sisters were free of cutaneous disorders or blemishes.

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native diagnosis. In syringocystadenoma, however, the little tumors are rarely if ever so deeply tinted (except when they occur in the negro, of which I have seen two examples); the tumors are not so sharply defined; their peripheries slope and the individual papules are frequently bordered by a narrow band of erythematous or pigmented skin; the endothelial tumors, on the other hand, were quite sharply demarcated, with abrupt peripheries; the elements of syringocystadenoma give the impression of being *in* the skin, while the endotheliomata in this patient readily impressed the observer as being *on* the skin.

With regard to the second patient, the infant, little more can be said except that the clinical diagnosis of urticaria pigmentosa was concurred in by a dozen competent dermatologists. Not until the microscope revealed the true state of affairs did anyone entertain the slightest suspicion that the eruption was composed of formations resulting from endothelial cellular proliferation.

As stated, McDonagh christened this dermatosis nevo-xantho-endothelioma. To those who are uninitiated in the complexities and niceties (?) of dermatological nomenclature the prefix, nevo-xantho may be a source of confusion. A nevus is a blemish which may be present at birth, may appear early in infancy and sometimes even in late adult life. "Xantho" refers, of course, to the yellow tint of the lesions. Now it so happens that urticaria pigmentosa is also known under the name of xanthelasma, on account of the close similarity, clinically, to the little tumors of xanthoma. Some eruptions of urticaria pigmentosa simulate xanthomata to such an extent that only a microscopic examination can tell them apart. McDonagh calls attention to the erroneous diagnosis of urticaria pigmentosa or xanthelasma applied to eruptions which proved (as in Case II), on microscopic examination, to be endotheliomata, appearing at birth or early in infancy. Hence the name, nevo-xantho-endothelioma.

In this connection attention should be called to the fact that the lesions in Case I also would by many pathologists be regarded in the light of nevi of endothelial origin. From the pathologist's point of view a nevus may make its appearance at any period in life; the pathologist's conception of the term embraces a far more comprehensive group of cutaneous anomalies than does that of the clinician; for example, ichthyosis, xeroderma pigmentosum, syringocystadenoma, benign cystic epithelioma, lymphangioma circumscriptum and several other morbid changes in the skin are by many considered to belong in the nevus group. This question, as already intimated, is still undecided. The whole subject is, I think, very interestingly discussed by McDonagh, in his chapter on "The Role Played by the Endothelial Cell in Inflammation and its Probable Relationship to Sarcoma." Most dermatologists will find this to be a rather refreshing bit of reading, and certainly well worth the while.

**HISTOPATHOLOGY** (see Figs. 3, 4, 5, 6, 7, 8, 9). Three tumors of different sizes and seemingly various ages were removed from Case I and one papule from Case II for purposes of microscopic study. These were sectioned and stained with hematoxylin-eosin, van Gieson, polychrome methylene blue, Unna-Pappenheim, acid-orcein and Weigert's elastic-tissue stains.



FIG. 3.—Case II. Endothelioma cutis. The eruption closely resembles urticaria pigmentosa.

The only noteworthy difference between the microscopic structures of the young and older lesions consisted in a correspondingly lesser or greater amount of cellular infiltration in the corium and in unimportant secondary changes in the epidermis, due to pressure exerted upon it by the underlying infiltrate. When the subepidermal infiltrate was sparse the epidermal layer was practically unaltered; when the infiltrate was abundant the covering epithelium was flattened and compressed. The sections here described were cut from a young lesion, and from another, apparently fully developed old lesion, taken from Case I, and from a fully developed pea-sized papule, taken from Case II.



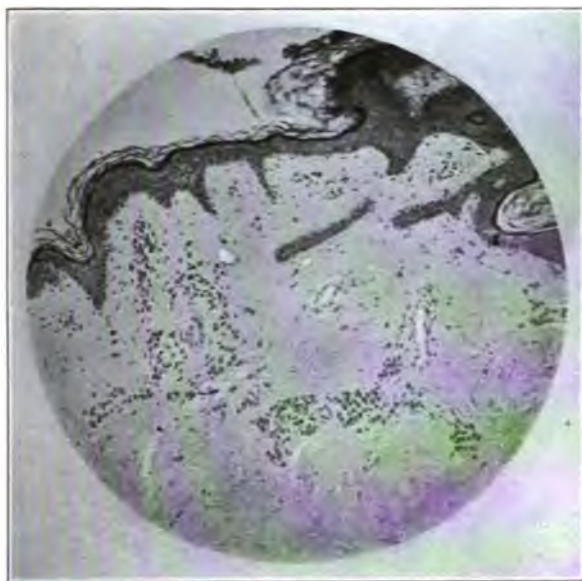


FIG. 4.—Case I. Endothelioma, early lesion showing derivation of cells.



FIG. 5.—Case I. Endothelioma, early lesion showing derivation of cells.

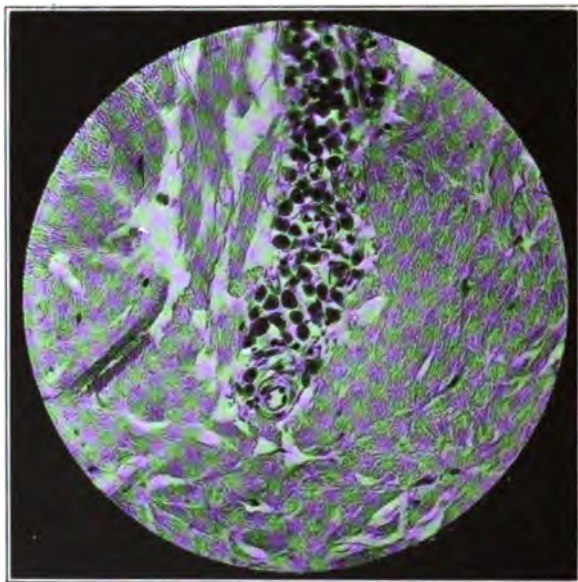


FIG. 6.—Case I. Endothelioma, early lesion showing derivation and type of cells.

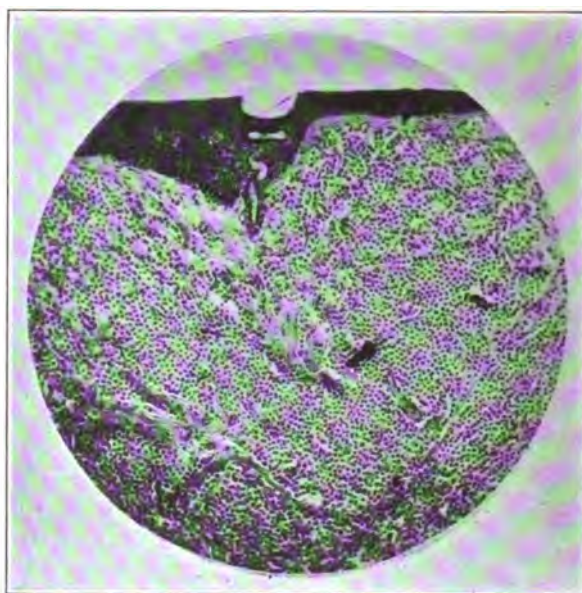


FIG. 7.—Case I. Endothelioma, late lesion showing widespread infiltration,

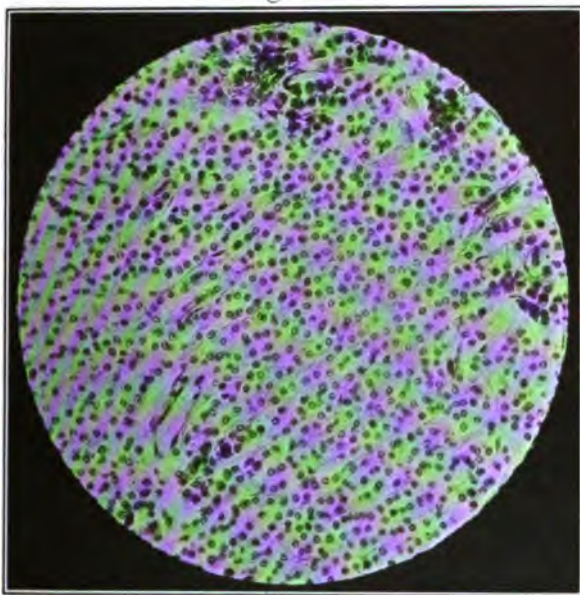


FIG. 8.—Case I. Endothelioma, late lesion showing type of cell.

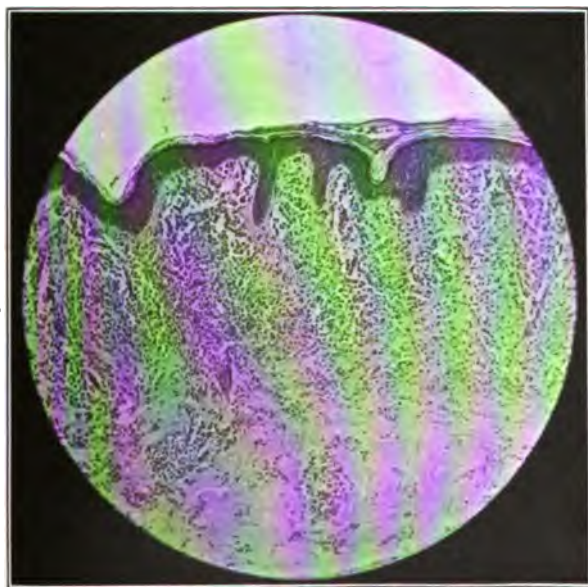


FIG. 9.—Case II. Endothelioma. The histopathology is almost identical with that of Case I.

Strikingly different as these three lesions appeared to the clinical eye they nevertheless presented practically identical pathological alterations under the microscope.

In the young growth the epidermis is but little altered; there is a moderate amount of hyperkeratosis and slight intercellular edema; in some places the basal layer presents a decided increase in pigment. In the corium there are irregularly disposed collections of cells, grouped mostly about blood and lymph vessels and filling the lymph channels and spaces. There is a moderate increase in the vascular supply, most pronounced in the upper half of the cutis.

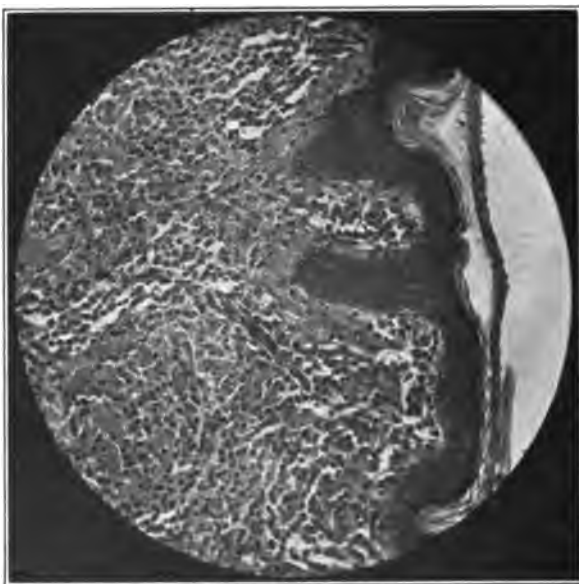


FIG. 10.—Case II. Endothelioma. High magnification of section of Fig. 9.

The connective tissue exhibits a mild grade of edema. Isolated cells and small groups of cells, morphologically identical with those composing the larger infiltrates, are scattered throughout the cutis, lying in the interfascicular spaces and in narrow lymph channels or clefts. The elastic tissue is diminished and fragmented.

In the older lesion the epidermis is decidedly thinned; the portion overlying the large area of subepidermal infiltration shows a complete absence of papillæ, the basal membrane forming a perfectly straight line. These changes in the epidermis are evidently due to pressure exerted by the underlying mass of infiltrating cells.

The upper two-thirds of the corium present a uniform, dense cellular infiltration. This mass of cells is roughly semicircular in

outline, the base of the semicircle opposite the basal layer of the epidermis, the peripheral segment rather sharply outlined against the adjacent, relatively cell-free and unaffected connective tissue of the deeper cutis. On either side of this infiltrate (on tangential section) the epidermis, relieved of pressure from below, resumes its normal appearance, maintaining the integrity of its papillæ. The dense cellular infiltrate embedded in the corium gives the impression of having displaced the connective tissue in the area occupied by it, an appearance intensified by the very sparse amount of connective tissue lying, in the form of fine fibrils and narrow strands, within the bounds of the cell mass. The upper boundary of the infiltrate is in some regions separated from the epidermis by a narrow band of compressed connective tissue; in other places the cells mingle with the lowermost layers of the epidermis, so that the sharp line of demarcation between epithelium and cellular infiltrate is lost.

This infiltrate is composed of closely massed cells of remarkably uniform shape and size. These cells possess a sharply defined, well-rounded, prominent nucleus and a distinctly outlined, round or oval, in some cases also polygonal cell body. The integrity of the protoplasmic body of the individual cells is maintained even where they are densely packed, so that a nice mosaic-like effect obtains. The morphological and tinctorial characteristics of these cells identify them as endothelial cells.

Although on superficial examination the disposition of the cell masses seems to bear no intimate relation to the structures lying within the confines of the infiltrate, closer inspection reveals the fact that they are grouped chiefly and most abundantly about the blood and lymph vessels. In some places the cells are ranged in vertical strands, separated by fine fibrils of connective tissue. In general these strands are disposed in a roughly radial fashion, like the outstretched fingers of the hand, the proximal ends lying in the papillary, the distal ends in the reticular portion of the cutis. There is a moderate increase in the vascular supply and a more pronounced increase in the lymphatic supply of the corium.

Under high power it is seen that the endothelial cells composing the infiltrate not only surround the blood and lymph vessels, but also occupy their lumina, in some places completely filling them, as well as the lymph channels, throughout the upper portion of the cutis.

The walls of the bloodvessels are not thickened; in fact, they appear to be unaltered save the proliferation of the intimal layer. The connective tissue of the corium, both within the infiltrating mass as also at its periphery, appears to be normal, aside from a moderate grade of edema. Evidences of hyaline degeneration are absent. The sebaceous and coil glands, of which the sections contain a few, are normal in appearance. The elastic tissue is



diminished in amount and fragmented throughout the entire cutis.

COMMENT. The outstanding feature in the histopathological structure of these little tumors is the cellular infiltrate, composed of endothelial cells, derived, in all probability, from the lining membranes of the blood and the lymph vessels in the corium.

The origin of these cells is the subject of much controversy in dermatopathological literature. To go into detailed discussion of the problem would be superfluous in this paper, for the readily accessible article on "Endotheliomata" by Zeit, the excellent monograph on *Skin Cancer* by Hazen and McDonagh's chapter on the "Endothelial Cell" deal fully with various phases of the subject and need not be transcribed here.

There can be no question that the histological picture herein described bears some points of similarity to certain types of carcinoma (rodent ulcer), sarcoma and so-called cylindroma, although when sections of these various tumor forms are studied side by side certain well-marked differences become immediately obvious.

Zeit points out the following differential histological features in carcinoma, sarcoma and endothelioma, incidentally emphasizing the character and disposition of the cells composing the infiltrate in the last-mentioned form of new growth:

1. "The tumor cells in endothelioma are intimately connected with the stroma and cannot be brushed out of the stroma, as in the case of carcinoma, in which the epithelial cells may also retract from the stroma and show spaces.

2. "Endothelial cells produce intracellular cement substance and are closely packed together, whereas the epithelial cells in carcinoma have no intercellular substance and form no compact layers.

3. "In endothelioma delicate fibrillar processes extend from the walls of the alveoli into the proliferated cell masses. They are absent in carcinoma.

4. "In endothelioma the cell masses consist of a dense mosaic of many layers of cells, with small, sharply outlined nuclei, surrounded by a broad envelope of clear, glassy perinuclear protoplasm. Carcinoma cells have large vesicular nuclei, with a moderate amount of perinuclear protoplasm, more or less granular.

5. "In endothelial tumors the cells are arranged in the form of cellular cords and cylinders (round masses in carcinoma) and may separate out hyaline material (cylindroma) or form lumina-like masses (sieve-like) in the cellular cords, due to secretory processes of endothelial cells.

6. "To distinguish the endothelial tumors from sarcomata it is to be remembered that the former have an organoid and the latter a histoid structure. According to this definition, every large-cell sarcoma with a well-developed stroma which was formerly called alveolar sarcoma would be called an endothelioma."

**CONCLUSIONS.** The type of endothelial new growth herein described is probably very rare, its literature being very scant. Most of the cases heretofore described were the so-called "turban tumors" of the scalp, first published by Ancell and later by Spiegler.

Clinically, tumors of endothelial origin may be indistinguishable from the efflorescences of urticaria pigmentosa, xanthoma, soft moles, syringocystadenoma, multiple benign cystic epithelioma and perhaps other dermatoses. The inference that the study of sections from cases of this kind would occasionally reveal new growths of endothelial origin seems justifiable.

The writer is indebted to Professor Fordyce for permission to publish the account of Case II from the dermatological department of the Vanderbilt Clinic, and to Assistant Professor MacKee for his kindness in supplying the photomicrographs.

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## CLINICAL RESULTS IN TWO HUNDRED TRANSFUSIONS OF CITRATED BLOOD

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**INTRODUCTION.** A little more than four years have elapsed since I first suggested the application of a minute dose of sodium citrate for use in blood transfusion. It seems to be the fate of every new suggestion in medicine that it encounters a great deal of skepticism. The citrate method was no exception to the rule. Experiments on animals<sup>1</sup> and a large series of cases in the human being (22 cases<sup>2</sup>) had proved the efficiency and harmlessness of this method beyond doubt. Yet most of the clinics in this country still continued to use the older and much more complicated methods (syringe-cannula method, paraffinized glass cylinders, etc.).

The skepticism, however, has vanished considerably in the last two years. It is safe to say that the vast majority of transfusions done in this country at the present time are citrate transfusions. The simplicity of the method, its safety and the efficiency were bound to appeal to the medical profession.

The Mayo Clinic was one of the first clinics to try this new method on a large scale. Their results are illustrated in the following note of

<sup>1</sup> Lewisoohn: A New and Greatly Simplified Method of Blood Transfusion, *Med. Record*, 1915, lxxxvii, p. 141.

<sup>2</sup> Lewisoohn: Citrate Method of Blood Transfusion, *Surg., Gynec. and Obst.*, 1915, xxi, p. 37.

Dr. Pemberton<sup>3</sup>: "For the past two years we have been using the citrate method, as recommended by Dr. Lewisohn, almost to the exclusion of others, and it has proved eminently satisfactory. During this time we have employed it in between 900 and 1000 cases, and in no instance where chemically pure citrate has been used has there been any untoward result attributable to the method. The simplicity and sureness of the technic, the safety of its employment and the proved therapeutic value of the citrated blood should recommend the method for a more general adoption."

A commission, consisting of surgeons and serologists, now in service in France, has recently investigated the different methods and has recommended the method of citrated blood as the method of choice, because it is the most practical "under war conditions." Their conclusions are the following: "Of the many available methods the citrate method has been adopted, because:

- (a) It is the simplest with respect to technic.
- (b) It is the simplest with respect to equipment.
- (c) It has given uniformly excellent results in a large number of cases and the presence of the citrate has resulted in no practical disadvantage.
- (d) It is less of an operation to both donor and recipient, for it seldom necessitates an incision over the vein.
- (e) It is virtually a medical procedure, thereby saving the surgical personnel for major surgical work in times of stress."<sup>4</sup>

**HISTORY.** The citrate method of blood transfusion, though only a few years old, has already a history of its own. It seems to be the trend of the human mind to work out new methods along complicated lines first and simplify them later. Ideas for possible improvements ripen very often in the minds of different investigators at about the same time. It was natural that the very cumbersome technic of the older methods of blood transfusion should stimulate research workers to simplify the technic; and it was further very natural that the idea of the use of anticoagulants should suggest itself as a very obvious way toward such simplification. As far back as 1908 this problem was approached by Lespinasse. In a discussion of Abelmann's paper on the technic of direct transfusion of blood, Lespinasse<sup>5</sup> said: "In 1908 and 1909 I convassed the problem (anticoagulants) thoroughly and found that peptone and hirudin are absolutely toxic and that sodium citrate in moderate amounts is quite toxic. In smaller amount it is not so toxic, but it is toxic. In hemorrhagic diseases any method that includes a non-coagulating element in the transfused blood is absolutely contra-indicated."

<sup>3</sup> Janeway: Blood Transfusion, Course of Instruction on War Surgery, Cornell University Medical School, 1918.

<sup>4</sup> A Report upon Transfusion of Blood for the Recently Injured in the U. S. Army, May, 1918.

<sup>5</sup> Chicago Med. Rec., 1915, xxxvii, p. 589.



I have never claimed any priority for the idea of using anti-coagulants in blood transfusion. For instance, sodium phosphate and sodium oxalate were tried as anticoagulants in blood transfusion in the last century, though without success, by Braxton Hicks<sup>6</sup> and Wright.<sup>7</sup>

However, it seems that it was my good fortune to show<sup>1</sup> that by using a minute dose of sodium citrate this anticoagulant could be used even for large blood transfusions without causing any toxic effects in the recipient. These experiments, furthermore, determined for the first time the maximal dose of sodium citrate for the human being (5 grams).

At exactly the same time (January, 1915), Agote,<sup>8</sup> of Buenos Ayres, published an article on the same subject. It is a peculiar coincidence that both these investigations went on at the same time and were published contemporaneously.

Agote's dose (0.25 per cent.) is perfectly safe and amply sufficient to prevent coagulation. His investigations, however, were less thorough, as he did not study the question of maximal dosage. Furthermore, his stock solution (25 per cent.) is too strong. Thus, during the collection of the initial 100 to 200 c.c. of blood the very strong concentration of his stock solution is apt to destroy vital elements of the blood.

A few months previous to our publications Hustin,<sup>9</sup> of Brussels, had published a report on the same subject. However, as Hédon has shown, his method and the results of his experiments have really not answered the problem in question: "He mixed in equal parts blood with an isotonic glucose-salt solution, containing a certain proportion of sodium citrate, and injected this mixture in small quantities. Thus, Hustin's method of transfusion is really an infusion of a strongly diluted blood mixed with citrate of soda and glucose." (Hédon.<sup>10</sup>)

The technic of citrate transfusion consists of two distinct steps: The first, that of properly preventing coagulation of the blood as it is collected from the donor, is the step of major importance. The second, that of its introduction into the blood stream of the recipient regardless of the type of apparatus used, is of distinctly minor importance.

The conclusiveness of the original experiments which were the basis of the citrate method (minimal and maximal dosage, etc.), made it apparent from the start that no important changes would

<sup>6</sup> Cases of Transfusion, with Some Remarks on a New Method of Performing the Operation, *Guy's Hosp. Rep.*, 1869, xiv, p. 1.

<sup>7</sup> A New Method of Blood Transfusion, *British Med. Jour.*, 1891, ii, p. 1203.

<sup>8</sup> Nuevre procedimiento para la transfusion del sangre, *Anales del. Inst. mod. de Clin. Med.*, 1915.

<sup>9</sup> Principe d'une nouvelle méthode de transfusion muqueuse, *Jour. Méd. de Bruxelles*, 1914, xii, p. 436.

<sup>10</sup> Note complémentaire sur la transfusion du sang citraté, *Presse méd.*, 1918, xxvi, p. 57.

be made by further investigations in this direction. On the other hand, it was to be expected that many new suggestions would be made in reference to the apparatus. The apparatus, as originally suggested by the author, seems to have the advantage of utmost simplicity. An ordinary glass jar and a salvarsan flask represent the essentials of this outfit. Pemberton,<sup>11</sup> Heyd,<sup>12</sup> Williams,<sup>13</sup> Graves,<sup>14</sup> Garbat,<sup>15</sup> McKay,<sup>16</sup> and many others have published their results and expressed their perfect satisfaction with the author's original technic. Later modifications by different authors (Singleton,<sup>17</sup> Stansfeld,<sup>18</sup> Mumey,<sup>19</sup> Janeway,<sup>20</sup> Zingher,<sup>21</sup> Abelman,<sup>22</sup> Jeanbrau,<sup>23</sup> etc.) have not acquired general popularity, as they are not more efficient than the simple outfit in its original form.

Special apparatus has the disadvantage of not being at hand when the emergency for blood transfusion may arise, whereas a graduated glass jar and a glass funnel with a piece of rubber tubing are always at hand, even in the smallest hospital, or can be procured from any drug store.

There can be no objection to individual surgeons using special outfits according to their preference. It is, however, not advisable to try to combine the application of sodium citrate with the older methods, either syringe method (Zingher,<sup>24</sup> Abelman<sup>25</sup>) or Kimpton-Brown glass cylinders (Jeanbrau<sup>26</sup>). The disadvantage of the Kimpton-Brown tubes is that the method requires exposure of the vein of the donor. To use these tubes in combination with the citrate method, as Jeanbrau has suggested, complicates the citrate method unnecessarily and would tend to make the method less popular.

Jeanbrau's work has helped a great deal toward popularizing the citrate method in France. Hédon<sup>27</sup> had worked out the experi-

<sup>11</sup> Loc. cit.

<sup>12</sup> Blood Transfusion, with Special Reference to the Citrate Method (Lewisohn), New York Med. Jour., 1917, cvi, p. 57.

<sup>13</sup> Lewisohn: Citrate Method of Blood Transfusion, etc., U. S. Naval Med. Bull., 1916, x, p. 503.

<sup>14</sup> Blood Transfusion in Anemia, Texas State Jour. Med., 1917, xiii, p. 137.

<sup>15</sup> Intravenous Injections of Sodium Citrate with Reference to Transfusion, Jour. Am. Med. Assn., 1916, lxvi, p. 1543.

<sup>16</sup> McKay-Lewisohn Method of Blood Transfusion, Med. Jour. of Australia, 1916, i, p. 217.

<sup>17</sup> A Reliable Method of Blood Transfusion, Southern Med. Jour., 1916, ix, p. 439.

<sup>18</sup> An Apparatus for the Transfusion of Blood by the Citrate Method, Lancet, 1918, cxliv, p. 334.

<sup>19</sup> Apparatus for Transfusion of Blood by the Sodium Citrate Method, Jour. Arkansas Med. Soc., 1917, xiii, p. 158.

<sup>20</sup> Loc. cit.

<sup>21</sup> A Simple Syringe Method for Transfusion of Blood in Children, New York Med. Rec., 1915, lxxxvii, p. 440.

<sup>22</sup> Blood Transfusion Simplified by the Use of Citrate Ointment, Surg., Gynec. and Obst., 1918, xxvii, p. 88.

<sup>23</sup> Technique simple du transfusion du sang stabilisé par le citrate de soude, Presse méd., 1918, xxvi, p. 58.

<sup>24</sup> Loc. cit.

<sup>25</sup> Loc. cit.

<sup>26</sup> Loc. cit.

<sup>27</sup> Loc. cit.

mental basis of the method, at the suggestion of Jeanbrau, and without knowing anything of the work done in this hemisphere. Both authors published their results in 1917. It is a great satisfaction that Hédon's conclusions coincide in practically every detail as to minimal and maximal dose, etc., with the author's results. Hédon and Jeanbrau have acknowledged Agote's and the author's priority claims. Jeanbrau's pupils (Murard,<sup>28</sup> etc.) have called the citrate method in a series of publications "la méthode de Jeanbrau." For reasons above given it seems advisable to adhere to the original name suggested by the author, "citrate method." Otherwise, we would in a very short time have the same method called by a dozen different names according to different apparatus used in its execution. As stated above, the important principle is the application of sodium citrate; modifications of apparatus are of minor importance.

**INDICATIONS FOR TRANSFUSION.** The following review is based upon the material of 200 transfusions (150 cases) which I had occasion to collect during the past three years. Such material is moderate in size compared to large series collected in the present war. However, it has the advantage of showing the usefulness of blood transfusion in a great variety of diseases, whereas the application of transfusion in the theater of war is limited to hemorrhage, shock and sepsis. The vast majority of the transfusions were performed at Mount Sinai Hospital. Some were obtained in private practice and others in different hospitals in New York (Roosevelt, Presbyterian, Beth Israel, Lebanon, St. Luke's, Lenox Hill Hospitals) in the early part of 1915, where I was asked to demonstrate this new method. I beg to thank the attending physicians and surgeons who had charge of the cases for their kind permission to use the records.

It is well known to what extent the technic of blood transfusion has been revolutionized during the past ten years. Crile's direct vessel anastomosis and Landsteiner's work on hemolysis and agglutination are monumental mark-stones in the development of the technic of blood transfusion.

The indications for blood transfusion, however, have changed very little during the last fifty years. A perusal of the literature (Belina-Swiontkowski,<sup>29</sup> Gesellius,<sup>30</sup> Jennings,<sup>31</sup> etc.) shows that in the middle of the last century transfusion was used in a great variety of diseases (hemorrhage, leukemia, hemophilia, CO poisoning, tuberculosis, eclampsia, etc.). To be sure, the usefulness of blood transfusion has been materially widened since the invention of safe methods for its performance. Very few new indications for blood transfusion, however, have been added in this era of technical perfection of blood transfusion.

<sup>28</sup> *La transfusion du sang veineux citraté par le procédé de Jeanbrau*, Lyon Chir. 1918, xv, p. 147.

<sup>29</sup> *Transfusion des Blutes*, Heidelberg, 1869.

<sup>30</sup> *Ibid.*, Petersburg, 1873.

<sup>31</sup> *Transfusion*, London, 1883.

It is not the object of this paper to discuss blood transfusion in all its different aspects. Ottenberg and Libman's paper<sup>32</sup> and Bernheim's<sup>33</sup> book published recently have covered the subject so extensively that a thorough presentation of the whole subject at the present time would simply mean a repetition. I therefore prefer to review some points of interest which I had occasion to observe in collecting the 200 cases of transfusion of citrated blood and to dwell on such points as to value and efficiency of the citrate method which are still subject to discussion.

TABLE I.—RESULTS OF TRANSFUSION OF CITRATED BLOOD.

Disease.	Number of cases.	Number of transfusions.	Cured.	Improved.	Not improved.	Unknown.	Died.
1. Hemorrhage:							
(a) Hemophilia and allied conditions . . .	14	15	11	..	..	..	3
(b) Purpura . . .	16	20	4	5	..	2	5
(c) Gastro-intestinal hemorrhage . . .	11	20	2	1	..	..	8
(d) Cholemia . . .	5	11	..	..	..	..	5
(e) Postoperative hemorrhage . . .	13	16	6	..	..	..	7
(f) Hemorrhage from female genital organs . . .	2	2	..	..	..	..	2
(g) Traumatic hemorrhage . . .	2	3	1	..	..	..	1
2. Diseases of the blood:							
(a) Pernicious anemia and leukemia . . .	24	39	..	7	4	..	13
(b) Primary and secondary anemia . . .	4	7	3	1	..	..	..
3. Preoperative and postoperative transfusions . . .	35	39	12	..	..	..	23
4. Sepsis . . .	5	7	..	..	..	..	5
5. Incurable conditions (transfusions performed at request of family) . . .	12	12	..	..	..	..	12
6. General debility . . .	6	8	..	1	..	1	4
7. Acute poisoning . . .	1	1	1	..	..	..	..
Totals . . .	150	200	40	15	4	3	88

In checking up the final results, such cases as were liable to die a short time after leaving the hospital, on account of the underlying disease (inoperable carcinomata, etc.), were put down as fatal results. Many of these cases leave the hospital temporarily strengthened on account of the transfusion. If they had been put down as "improved," as has been done in many other transfusion statistics, the death rate would have been lowered considerably. Furthermore, we have tried to follow up the final results in our cases. Thus a considerable number of cases which appeared to be cured or considerably improved upon discharge, but died subsequently at home on account of a recurrence of their original disease, were put down as fatal results.

<sup>32</sup> Blood Transfusion, AM. JOUR. MED. SC., 1915, cl, p. 36.

<sup>33</sup> Blood Transfusion, Hemorrhage and the Anemias, 1917.

## 1. HEMORRHAGE.

The prime indication for blood transfusion will always be the restitution of blood lost in a profuse hemorrhage. The great therapeutic usefulness of transfusion in hemorrhage is, of course, not limited to hemorrhages caused by traumatic injuries to large vessels, but comprises just as well the hemorrhages occurring in typhoid fever, ectopic pregnancy, ulcer of the stomach, etc., and in hemorrhagic diseases (hemophilia, melena, etc.).

(a) *Hemophilia and Allied Conditions* (14 Cases, 15 Transfusions; 11 Cures, 3 Deaths).

The indication for transfusion in these cases was very profuse hemorrhage, seriously endangering the life of the patient. Nine of the patients were newborn babies, suffering from hemophilia neonatorum. They were all extremely exsanguinated and would have died in a few hours without a transfusion. A single transfusion saved six of these babies. Methods of procedure and the wonderful permanent cures obtained in these newborn infants have been discussed in a previous paper.<sup>24</sup>

Among the remaining 5 cases, 3 concerned children (two and one-half, three and eight years of age, respectively). The father of one child was a bleeder, the others did not come from bleeder families, yet they bled so profusely from small wounds, which ordinarily should have stopped bleeding spontaneously, that they were evidently hemophiliacs. Very little is known at the present time about the true status of this disease, and our diagnosis is mostly based upon the clinical symptoms of protracted bleeding from small wounds. In every one of these cases thromboplastin and horse serum had been tried, before transfusion had been resorted to. Horse serum, thromboplastin, coagulen, etc., are not nearly as effective as transfusion of blood. Though exact figures are not at hand, they seem to be effective, according to the personal experience of the author and reports in the literature, in about 30 per cent. of hemophiliac bleeding. They ought to be tried in every case. However, if they are not effective blood transfusion ought to be immediately resorted to without loss of valuable time.

In 2 of these cases the hemorrhage stopped immediately after one transfusion and the other required four transfusions before the curative effect was obtained. In the emergency of the first transfusion, while the patient is extremely exsanguinated and no available donor at hand, members of the family (after proper tests) are usually used as donors. If the first transfusion has not the desired

<sup>24</sup> Lewisohn: Blood Transfusion (Citrate Method) in Hemophilia Neonatorum, *Am. Jour. Obst.*, 1918, lxxvii, p. 933.

effect, professional donors ought to be taken. It is a well-known fact, no matter what the primary disease may be, that if the first transfusion is not effective a second transfusion may stop the hemorrhage, if a different donor is obtained. The reason for this interesting and important observation is not known. However, its actual correctness has been noticed in many cases by different observers. Yet this fact, of vital importance as it is, is often overlooked, thus possibly causing death, where a perfect cure might have been obtained. Transfusion of blood, simple as it may seem, if we look at it from the purely technical point of view, requires thorough knowledge and strict observance of many fine points in order to obtain really good clinical results.

One of the few cases in this series of 200 blood transfusions, in which transfusion had to be resorted to without previous test for hemolysis and agglutination, was a boy, aged eleven years, who was admitted to Beth Israel Hospital with a large hematoma of the scalp following a slight injury. His maternal grandfather had died at the age of thirty-five from some uncontrollable hemorrhage. The boy had noticed the swelling four days before his admission to the hospital. As no facts about his bleeding tendency were known when the boy was admitted, and as the boy showed a marked protrusion and edema of the right eye (pressure from retrobulbar hematoma), an immediate incision about one and a half inches long was made through the skin above the swelling and a large collection of sanguinolent fluid drained off. No outward signs of bleeding followed. However, when I reached the hospital the next morning the boy was practically pulseless, as white as a sheet, showed extreme air-hunger, and was evidently in a dying condition. Luckily his father was standing at his bedside. Without any tests, 350 c.c. of blood were taken from the father and inside of fifteen minutes, after I reached the hospital, the boy had received this quantity of blood, which ensured his perfect recovery. In such a case minutes count, and if we had not used great speed the boy might have died before the blood was introduced into his veins.

The last case of this series, a man, aged thirty-two years, offered some points of interest as to his family history and as to the change of coagulation time following citrate transfusion. He told us that he had lost three brothers and six cousins (children of his mother's two sisters) following a ritual circumcision. Such a mortality is appalling. All these deaths occurred twenty to thirty years ago. Each one of these lives could probably have been saved by a single transfusion. I relate these facts here to point out the importance of transfusion of blood. Many physicians, even at the present time, consider blood transfusion as a somewhat spectacular and rather useless procedure. Here were nine lives wasted because the accidents occurred many years ago, before transfusion had been properly developed.

The coagulation time of this patient's blood before the transfusion was two and a half hours; twenty-four hours after the citrate transfusion it was only fifteen minutes. Tests taken three days later showed that it had come down to normal (five and a half minutes). If tests had been taken two weeks later they probably would have shown that the coagulation time had gone back to its previous state. As explained in a previous paper on this subject,<sup>26</sup> the shortening of the coagulation time is only temporary; it usually returns to its pre-transfusion stage in twenty-four to forty-eight hours.

(b) *Purpura Hemorrhagica* (16 Cases, 20 Transfusions; 4 Cures, 5 Improved, 2 Results Unknown, 5 Deaths).

We have in the previous chapter (hemophilia) confined ourselves to the discussion of one clinical symptom (hemorrhage) and its treatment by transfusion of blood. In the same way the discussion of purpura hemorrhagica must be limited to the investigation of results obtained by transfusion following profuse hemorrhages. A presentation of the pathological changes and clinical symptoms in purpura hemorrhagica would go far beyond the scope of this paper.

Blood transfusion in purpura is not nearly as effective as in hemophilia. It seems that some cases of hemophilia can be permanently cured, especially if done in infancy, by a single transfusion. The introduction of normal blood seems to repair the defect in the thrombus-forming mechanism and may thus result in a permanent cure. Results obtained in transfusion of purpuric patients are very unsatisfactory. In the majority of cases transfusion does not seem to influence the progress of the disease materially, though temporary benefit can be obtained. Thus cures in chronic purpura cannot be considered as permanent, though some of the patients were apparently in perfect health two years after the transfusions. Remissions of long intervals are frequently observed in purpura.

The predominant symptoms in five cases were very profuse menstrual bleeding, lasting for several weeks and so profuse that it very seriously endangered the life of the patient. The clinical significance of these menstrual flows, generally occurring in young girls between the ages of eighteen and twenty-four years, is very often overlooked by the general practitioner or gynecologist who tries to cure these cases by local treatment. Even hysterectomies have been performed to stop these hemorrhages.

Two of these girls had, in addition to the uterine bleeding, hemorrhages from nose, throat and gums, and their skin was scattered with

<sup>26</sup> Lewisoohn: Importance of Proper Dosage of Sodium Citrate in Blood Transfusion, *Ann. Surg.*, 1916, lxiv, p. 618.

ecchymotic spots. One of them was perfectly well two years later, the other died very soon after the transfusion. In the three other cases the bleeding stopped temporarily; however, we did not think that the transfusions were of material benefit.

Six cases of purpura were encountered in children under fifteen years of age; two of them died and two were improved when they left the hospital.

Excellent results following transfusion were obtained in two children suffering from acute purpura. A child, aged seven and a half years, had profuse nose bleeding and had vomited large quantities of blood (clinical diagnosis: morbus maculosus Werlhofii). Injections of horse serum were ineffectual, whereas one transfusion gave a marvellous result. The bleeding stopped immediately and the hemoglobin rose from 34 to 58 per cent. and the platelets increased to 104,000.

The other case presented a very rare condition, *i. e.*, acute purpura following chicken-pox. The boy, aged twelve years, had had chicken-pox, which seemed to run its normal course. On the tenth day of the disease all the pustules suddenly turned hemorrhagic. In addition he had profuse intestinal hemorrhages, which practically exsanguinated the boy. The condition was so serious that we had to transfuse him in the middle of the night. The father and mother were tested and the mother was used as donor. The boy seemed out of danger, when thirty-six hours later another profuse hemorrhage necessitated a second transfusion, the blood being taken from an aunt. Though the boy's life seemed to be ebbing away, this transfusion saved him. Bleeding stopped entirely and he made an uneventful recovery.

Transfusion results in purpura in the adult male were very unsatisfactory. One case made a very excellent recovery, two died in the hospital, whereas the others left the hospital upon request soon after the transfusion, without real improvement.

(c) *Gastro-intestinal Hemorrhage (11 Cases, 20 Transfusions;  
2 Cures, 1 Improved, 8 Deaths).*

Hemorrhages from the gastro-intestinal tract are a very frequent indication for blood transfusion. Gastric hemorrhages especially often reach such alarming proportions that transfusion must immediately be resorted to. The prognosis depends entirely upon the causative factor of the hemorrhage. If we are dealing with an ulcer of the stomach an operation should be performed immediately after the transfusion. The combination of transfusion and immediate gastric operation gives very good clinical results. Cases of this character do not appear in this group but are reviewed in a subsequent chapter on preoperative transfusions.

However, it would be erroneous to assume, as is often done, that



the cause for a profuse gastric hemorrhage must necessarily be an ulcerative process in the stomach. It should not be overlooked that the real cause for a gastric hemorrhage is very often extra-gastric (spleen, liver, appendix, esophagus, etc.). In these cases an exploration of the stomach fails to show any pathological changes. We encountered two such cases, with negative stomach findings, on exploration. Both these cases have been previously reported by Dr. Moschcowitz.<sup>36</sup> One of them, a nurse, made an uneventful recovery. She has been perfectly well for three years. The cause of her most alarming hemorrhages has never been established. The other case, a child, received eleven transfusions (five of them by the citrate method) in the course of three years, on account of repeated and very profuse gastric hemorrhages. Exploration of the stomach was entirely negative. The hemorrhages persisted and recurred at intervals of from three to six months. In the latter part of her illness the spleen showed considerable enlargement, thus giving the first clue as to the real cause of the hemorrhages. Post-mortem examination showed that the child had been suffering from Banti's disease. Splenectomy, as described by Balfour, would have been the only proper procedure to cure this little girl. However, when the diagnosis was made she was in such a weakened condition that operative interference was out of the question. It is evident that the transfusions could give only temporary relief. In another case, cirrhosis of the liver was the evident cause of the gastric hemorrhage. Transfusion was done as a last resort, but did not change the ultimate fatal outcome.

Three cases with a typical ulcer history of some years' duration and sudden very profuse hemorrhages required transfusion. The decision as to when to transfuse these cases is not an easy one. Many of the older text-books advise not to replace the lost amounts of blood by any intravenous injection. They claimed that a very low blood-pressure was necessary to give the ulcer a chance to heal and that a patient with a bleeding ulcer must be practically exsanguinated before he could recover. They maintained that a gastric hemorrhage, alarming as it may seem at the moment, will not cause death, but always stops automatically. This assumption, however, is incorrect. It cannot be denied that some patients will recover spontaneously even after very profuse hemorrhages. However, it is not safe to wait too long, on the assumption that Nature will take its course and safeguard an ultimate recovery. Death from gastric hemorrhage is by no means infrequent. If the blood-pressure falls below 80 mm., if the patient's lips become white or livid and his pulse becomes very rapid, an immediate transfusion followed by an operation, if possible, becomes extremely urgent. The combination of transfusion and operation offers the best

<sup>36</sup> Massive Hemorrhages from the Stomach without Demonstrable Ulcer, *AM. JOUR. MED. SC.*, 1916, clii, p. 714.

chances for absolute recovery. We lost two cases in spite of repeated transfusions, because we hesitated to explore immediately on account of the general condition of the patient. The hemorrhages recurred and the patients, who seemed to have been materially improved after the transfusions, died suddenly from recurrent hemorrhages before the source of the bleeding could be properly attacked.

One case seemed perfectly well after three transfusions, without recurrence of bleeding and with loss of all gastric symptoms (observation time four weeks). It is impossible to fix any definite rules about transfusion in hemorrhages. However, it seems that Bernheim's<sup>27</sup> advice is a very wise one: "When in doubt, transfuse." Nothing is lost and a great deal may be gained by a transfusion given at the proper moment.

In one case of inoperable gastric carcinoma with profuse hemorrhages, the bleeding stopped after one transfusion and the patient left the hospital temporarily improved.

We had three cases of intestinal hemorrhages. The first case was suffering from ulcerative colitis. Neither repeated transfusions nor a colostomy stopped the hemorrhages and the patient died. The other two cases were severe cases of typhoid with profuse hemorrhages. Transfusions stopped the hemorrhages, but both cases died ultimately from sepsis.

*(d) Cholemia (5 Cases, 11 Transfusions; 5 Deaths).*

Transfusion of blood in cases of jaundice is a very efficient and frequently applied remedy. As a preoperative measure it will materially increase the patient's chances for a speedy recovery. Applied postoperatively, to combat alarming oozing from the wound, it will often stop the hemorrhages like magic. The reason why we had 100 per cent. mortality in this group is based upon the fact that we were dealing with very complicated cases, not with cases of simple jaundice, caused by a common-duct stone.

Case 1: Common-duct stone; choledochotomy; secondary gastro-enterostomy for periduodenal adhesions.

Case 2: Biliary fistula following pylorotomy and gastro-enterostomy; second operation: drainage of common duct; third operation: cholecystoduodenostomy.

Case 3: Choledochotomy; biliary fistula; choledochoduodenostomy.

Case 4: Congenital stenosis of common duct in a child; cholecystostomy; bleeding from mouth, gums, rectum (hemorrhagic diathesis); five transfusions; temporary improvement; death.

Case 5: Hepaticoduodenostomy for common duct obstruction.

<sup>27</sup> Limits of Bleeding Considered from the Clinical Standpoint, *AM. JOUR. MED. SC.*, 1917, cliii, p. 575.

Transfusions were very beneficial in every one of these cases. However, the lives could not be saved, as the very complicated surgical procedures failed to establish normal anatomical conditions, thus causing ultimate death.

(e) *Postoperative Hemorrhages (13 Cases, 16 Transfusions; 6 Cures, 7 Deaths).*

We have collected in this group those cases in which hemorrhage followed operative interference and was entirely due to the trauma incidental to the operation (imperfect primary hemostasis, secondary hemorrhage, etc.).

Hemorrhage is not infrequent as a postoperative complication in gastric surgery, not only in cases of resection, but occasionally in simple gastro-enterostomies. An immediate transfusion of blood may save the life of the patient. We had two such cases, one following a partial resection of the stomach for ulcer of the lesser curvature and the other following a gastro-enterostomy. Both patients were in most serious condition and practically pulseless when the transfusion was given, and both made a rapid and uneventful recovery. In five cases (three ulcers and two carcinomata) transfusion was of temporary benefit only and did not prevent a fatal outcome.

Two patients with hemorrhages following operation on the genito-urinary tract were cured by transfusion, one occurring on the thirty-eighth day following a nephrectomy for tuberculous pyonephrosis. The wound which had been sluggish and necrotic assumed very soon after the transfusion a normal aspect and the patient's recovery was a rapid one.

Two children had profuse hemorrhages following operations for osteomyelitis of the femur; one of them was cured.

Two transfusions were given, with good result, in a nasal hemorrhage following resection of the turbinate bone.

In a case of profuse hemorrhage following an incision of a pylephlebotic liver abscess the bleeding stopped following the transfusion. However, the boy died a few days later from the primary condition.

(f) *Hemorrhages from the Female Genital Organs (2 Cases, 2 Transfusions; 2 Deaths).*

The importance of blood transfusion in ruptured ectopic pregnancy is by no means negligible, though our series has one case only. In cases of sudden profuse hemorrhages blood transfusion ought to be resorted to contemporaneously with immediate operation. While the surgeon is stopping the hemorrhage, new blood should be introduced into the circulation. The mortality can thus be reduced materially. It would be unwise, for obvious reasons, to introduce the blood

before the operation. Transfusion can only be effective after the bleeding vessels have been properly tied. The cause of death in our case was imperfect hemostasis.

The second case died from profuse operative hemorrhage based on a chorioepithelioma. The enormous bleeding was unexpected, no donor was at hand and a colleague (Dr. London) who happened to be present at the operation acted as donor.

(g) *Traumatic Hemorrhages (2 Cases, 3 Transfusions; 1 Cure, 1 Death).*

We encountered only two cases of hemorrhages following severe trauma. The subject of traumatic hemorrhage and its proper treatment has assumed vast proportions in the present war and has been extensively discussed in the last few years by a great many army surgeons. The reader is referred to those publications in which indications and results are discussed extensively, based upon an enormous material.

## 2. DISEASES OF THE BLOOD.

(a) *Pernicious Anemia and Leukemia (24 Cases, 39 Transfusions; 7 Improved, 4 Not Improved, 13 Deaths).*

Up to the present time diseases of the blood were considered a very promising field for the application of blood transfusion. However, the results obtained are, if considered critically, very discouraging. Among 24 cases of pernicious anemia and different forms of leukemia (acute leukemia, acute myelogenous aleukemia, lymphatic leukemia, chronic leukemia, etc.), 13 died, 4 were not improved and 7 showed a temporary improvement. We have lately, based upon our own unsatisfactory experiences and those of others, discouraged the use of blood transfusion in all forms of leukemia. Temporary short improvement is usually followed by a rapid exacerbation of the disease.

Results obtained in pernicious anemia are somewhat better, as long remissions of comparatively good state of health can be obtained by repeated transfusions. However, blood transfusion in these cases can only be considered a temporizing, not a curative measure. Results obtained by blood transfusion in the early stages of the disease are often very promising and the intervals between remissions of rather long duration. However, the intervals get shorter and shorter, with the progress of the disease, and the efficiency of blood transfusion, even when resorted to frequently, decreases rapidly, while the disease runs its fatal course. Splenectomy has been of benefit in a few single instances only. The vast majority of cases succumb in the course of two years (and often in a much shorter period) in spite of transfusions or splenectomy.

(b) *Primary and Secondary Anemia (4 Cases, 7 Transfusions; 3 Cures, 1 Improved).*

Excellent results were obtained in the few cases of primary and secondary anemia which came under our observation. When they entered the hospital, the patients appeared to be desperately ill on account of the severe anemia. They made a rapid recovery after the transfusion.

3. PREOPERATIVE AND POSTOPERATIVE TRANSFUSIONS (35 CASES, 39 TRANSFUSIONS; 12 CURES, 23 DEATHS).

Blood transfusion ought to be employed much more frequently as a preoperative and postoperative measure. Surgeons have in the last thirty years gradually widened their indications. Patients who are in a debilitated general condition ought to receive the benefit of a transfusion before they undergo large operations. They will stand the operative shock much better and their period of recovery will be shortened. In the same way a postoperative transfusion will often have the most marvellous effect. Instead of infusing large quantities of saline solution into the body, either subcutaneously or intravenously, a transfusion of blood ought to be given if alarming symptoms appear in the postoperative course. In fact, it is advisable to have a suitable donor available before the operation in case of emergency. It is not advisable, except in cases of profuse hemorrhage (ectopic pregnancy, etc.), to transfuse during the operation on account of the possibility of chills following the transfusion. It is an interesting fact that when blood is given following acute profuse hemorrhages chills do not occur.

By making extensive use of transfusions as a preoperative measure, eight patients, who were extremely bad operative risks, were saved. Among the fourteen deaths encountered in this series, 10 were based on the underlying condition, inasmuch as the operation revealed an inoperable malignant growth. By applying blood transfusion postoperatively, four lives were saved which were in extreme danger of passing away (empyema, acute mastoiditis, osteomyelitis of femur and pus kidney). The last case was in extreme condition following a simple incision and drainage of a pus kidney. 500 c.c. of blood taken from the husband of the patient changed the aspect entirely. She made an uneventful recovery not only from this operation, but from a subsequent nephrectomy.

Among the cases not saved were two lobectomies for lung abscess, one splenectomy for Gaucher's disease and one inoperable carcinoma of the liver.

4. SEPSIS (5 CASES, 7 TRANSFUSIONS; 5 DEATHS).

The treatment of acute forms of sepsis by blood transfusion is a perfectly useless procedure and our experience of 100 per cent.

mortality coincides with those of other observers. Sad as these cases are we must recognize that transfusion will not alter the prognosis. Whether the use of blood from immunized donors, as suggested by Hooker,<sup>38</sup> will be of help, remains to be seen. There can be no doubt that the use of donors, who have acquired immune bodies by successfully combating the same disease previously, offers a somewhat hopeful outlook. However, the scarcity of these donors, especially as far as sepsis is concerned, will always stand in the way of its general usefulness. If anything can help an acute sepsis it must be done immediately. Time will be lacking to immunize a donor artificially. The use of blood of convalescent patients in the treatment of measles and typhus fever has been suggested by Ribadeau-Dumas and Brissaud<sup>39</sup> and Escluse.<sup>40</sup>

An occasional case of acute sepsis will recover automatically. I had occasion to observe such a case. A woman developed an acute bacteriemia with positive blood culture, following a gynecological operation. We were ready to transfuse her and held back at the last moment, because she was slightly improved. She made a somewhat stormy recovery and was perfectly well after a few weeks. If we had given her the transfusion as planned, we would naturally have concluded that transfusion had saved her life.

On the other hand, cases of subacute and chronic sepsis are very much benefited by blood transfusion, and results obtained by this procedure are often really marvellous.

5. INCURABLE CONDITIONS (TRANSFUSIONS PERFORMED AT REQUEST OF FAMILY); (12 CASES, 12 TRANSFUSIONS; 12 DEATHS).

Transfusion has acquired such popularity among the laity that we are often forced to resort to it against our better judgment, in order to ease the mind of the sorrow-stricken family. We thus used transfusions in seven carcinomatous patients in the last stage, one case of third degree burns, admitted to the hospital in a dying condition, three cases of peritonitis and one case of sepsis, caused by an acute osteomyelitis of the femur.

6. GENERAL DEBILITY (6 CASES, 8 TRANSFUSIONS; 1 IMPROVED, 1 RESULT UNKNOWN, 4 DEATHS).

Two cases of malnutrition in infants were tested as to the value of transfusion. We agree with other observers that transfusion does not help these little infants. They succumb to a serious disturbance of the metabolism in spite of the transfusions. Transfusions with

<sup>38</sup> Treatment of Staphylococcus Septicemia by Transfusion of Immune Blood, *Ann. Surg.*, 1917, lxi, p. 513.

<sup>39</sup> Transfusion in Measles, *Bull. de la Soc. méd. des hôp. de Paris*, 1918, xlii, p. 147.

<sup>40</sup> Essai de traitement du typhus exanthématique par injections intraveineuses de sang vivant de convalescent, retardé dans sa coagulation par citrate de soude *Presse méd.*, 1915, xxiii, p. 450.

previous venesection were tried in 2 cases of acute nephritis. Results seem to be somewhat promising. However, the number of cases is too small to draw any definite conclusions.

#### 7. ACUTE POISONING (1 CASE, 1 TRANSFUSION; 1 CURE).

We had one brilliant result in a two-year-old boy who was admitted to the hospital in a dying condition, suffering from acute poisoning of unknown origin. He had slight air-hunger, showed extreme pallor and some purpuric spots on his legs and had passed bloody urine for twenty-four hours. Immediate transfusion saved his life. His hemoglobin rose from 15 to 50 per cent. following the introduction of 300 c.c. of blood taken from the father. His recovery was rapid and uneventful.

**GENERAL CONSIDERATIONS.** It is not advisable to advocate large transfusions. They may overstrain the heart and cause the death of the patient. Except in cases of profuse hemorrhage the average transfusions should range between 500 and 700 c.c. Very large ones are not more effectual clinically than medium-sized ones. Formerly large transfusions were quite en vogue. However, the simplicity of modern technic makes repetition of transfusion an easy matter and has replaced single large transfusions by repeated transfusions of medium size.

Nothing definite is known about the fate of the donor's blood after its introduction into the recipient. We do not know how long it preserves its own vitality nor when it is assimilated by the recipient's blood. That in a great many instances it acts as a stimulant for the blood-producing organs of the recipient can be seen from the fact that many cases show a rapid automatic rise of the hemoglobin a few days after the transfusion. This result is obtained just as effectively by medium-sized as by large transfusions.

The general popularity which the citrate method has acquired in the last year makes it unnecessary to enter into long discussions as to the relative values of citrated blood to non-citrated blood. It has been established beyond doubt that the clinical efficiency of the citrate method is absolutely equal to any other method of blood transfusion. Many authors have tested the relative values of the different methods by using various methods on the same patient (Bernheim,<sup>1</sup> Garbat,<sup>2</sup> author, etc.), and have shown that results obtained by the citrate method are just as good as those obtained by the older and more complicated methods.

It seems hardly fair to group the other methods as methods applying pure, unmodified blood, as has been done by some authors, in contradistinction to the citrate method. Citrated blood is just as

<sup>1</sup> Sodium Citrate Blood Transfusion. A comparison. Jour. Am. Med. Assn., 1917, 69, 359.

<sup>2</sup> Sodium Citrate Transfusions. A study of 100 cases. Jour. Am. Med. Assn., 1919, 72, 1.

pure as non-citrated blood. One of the most efficient and life-saving qualities of the blood is its tendency to coagulate. The possibility of existence of the human being is based on this fact. However, it was just this coagulation tendency of the blood which stood in the way of a development of a simple technic for blood transfusion. There can be no doubt that during the transfer of blood from donor to recipient the coagulation tendency of the blood is useless and unnecessary. The effectiveness of sodium citrate is based upon the fact that it changes temporarily during the transfusion this coagulating tendency of the blood without changing any of its other qualities.

The amounts of sodium citrate used with this method are so small that they do not play any role in the chemical and clinical properties of the recipient's blood. "Even after profuse hemorrhage there is enough calcium left in the bloodvessels and in the lymph for re-establishment of coagulation conditions in the transfused blood" (Sabattani<sup>43</sup>). In other words, the mixture of sodium citrate is efficient as anticoagulant only while the blood is outside the body. Soon after its introduction into the recipient the coagulating efficiency of the transfused blood is fully reestablished. It is probable that the sodium citrate is either changed or rapidly excreted by the kidneys.

The frequency of chills following transfusion does not seem to vary much according to the different methods used. In a series of 280 transfusions, Meleney, Stearns, Fortune and Ferry<sup>44</sup> observed the same percentage of reactions with the citrate method as with the syringe-cannula method. They conclude that the method of transfusion has nothing to do with the occurrence of the reaction.

According to the experience of the author and of others, chills occur somewhat more frequently with the citrate method than with other methods of blood transfusion. In our series of 200 transfusions we encountered chills in 40 cases (20 per cent.). The reasons for these chills, if proper blood tests were made before the transfusion, are not quite clear. I have repeatedly seen that in the same person citrate transfusions did not cause any chills, whereas subsequent transfusions of non-citrated blood caused acute rise of temperature with chills, and *vice versa*.

It is interesting to note that in the first 22 transfusions of our series no chill occurred. Furthermore, I have never observed a chill following transfusion given to children, even when rather large amounts of blood, as compared to the body weight, were introduced. No chill was encountered in any of those cases in which transfusion was given following a profuse hemorrhage.

It is by no means impossible that future investigators may find

<sup>43</sup> Calcium and citrate trisodique dans la coagulation du sang, de la lymphe et du lait, Attidella R. Accademia della Sc. de Torino, 1900, 36.

<sup>44</sup> Post-transfusion Reactions, AM. JOUR. MED. SC., 1917, cliv, p. 733.



another anticoagulant which may possibly diminish the percentage of chills. However, it is safe to say that the principle of the method (application of an anticoagulant for the simplification of the technic of blood transfusion) will prove of permanent value. ] The application of this principle has transformed transfusion from a very cumbersome and difficult method into a most simple procedure. Blood transfusion at the present time is not any more in the hands of a few specialists, but within the reach of every practitioner. By the immediate application of this simple method of blood transfusion in emergency cases a great many lives can be saved, especially in small communities, where the performance of the older, more complicated methods was out of question.

### A REPORT OF THE PATHOLOGICAL CHANGES OF THE BRAIN IN 162 CASES OF PARESIS.

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THE pathological changes of the brain and meninges found in paresis are based on 162 postmortem examinations on cases of paresis performed at the Norristown State Hospital. The diagnoses of the cases are from the clinical records and the diagnoses are based on careful histories, physical and mental examinations, and the more recent cases on the recently developed study of the blood and spinal fluid—as the cell count, Alzheimer's method for differential count, Noguchi's, Pandey's and Nonne's tests for protein content in the fluid, the Wassermann test on the blood and cerebrospinal fluid and the Lange colloidal gold test. By the routine use of these methods errors in differential diagnosis between cerebral syphilis and non-specific disorders are practically impossible.

The more recent cases of autopsies that have been diagnosed as paresis show 100 per cent. of positive Wassermann tests on the blood and spinal fluids. Plaut<sup>1</sup> describes two negatives among 320 sera, practically 100 per cent. positive, while in 276 cerebrospinal fluids 9 were negative and 96 per cent. positive. Boas found the Wassermann reaction positive in 100 per cent. of 243 cases. Ross and Jones<sup>2</sup> found their reaction positive in all their cases of paresis. Turner<sup>3</sup> examined 78 cases and found a negative reaction in 2 cases only. Boyd<sup>4</sup> found 8 positive reactions in 8 cases. Fildes and McIntosh<sup>5</sup> found the Wassermann positive in 98 per cent. of the cases of paresis. Among 143 cases of paresis, Lowery<sup>6</sup> found the

<sup>1</sup> Ztschr. f. d. ges. Neurol. u. Psychiat., original, 1911.

<sup>2</sup> British Med. Jour., 1909, i, p. 1111.

<sup>3</sup> Jour. Ment. Sc., 1910, lvi, p. 485.

<sup>4</sup> Ibid., 1912, lviii, p. 203.

<sup>5</sup> Syphilis from the Modern Standpoint, London, 1911, p. 117.

<sup>6</sup> Am. Jour. Insanity, April, 1916, lxxii.

blood test positive in 87.5 per cent. and negative in 10.3 per cent. Noguchi compiled the results of 26 different observers, who found positive serum reactions in 84.5 per cent. of 660 cases and 91 per cent. findings in 481 spinal fluid examinations. These percentages are probably below the correct findings unless examinations of the serum on fluid were made at repeated intervals, as in all the cases of undoubted paresis it has been my experience to find 1 or 4 of the 4 tests positive while most gave all 4 tests positive. The current literature contains many references and reports upon this subject. In most of the cases examined by the writer the typical Wassermann reaction was found present, which Kaplan<sup>7</sup> refers to as the "Wassermann-fast" phenomenon.

Generally speaking, the findings thus observed are in advanced cases, some extending over many years, with periods of remission. Among these cases some have been found which have shown a combination of paresis with other specific lesions. Probably none of the findings in paresis are pathognomonic, as the pathology found is due to irritating agents, and in these cases it is supposed to be due to the *Treponema pallidum*. It seems that an inflammatory process is behind every form of syphilitic involvement and that the spirochetes are at the bottom of the reaction. When a spirochete, as shown by Noguchi and Moore,<sup>8</sup> appears in the nervous tissues there is a double reaction: (1) of the nerve cells (parenchyma) and neuroglia (fixed interstitial cells) and (2) of the wandering cells. The inflammatory reaction is in direct proportion to the kind of tissue involved. There is every reason why the meninges respond more violently than the parenchyma of the brain. The reaction of vascular interstitial tissue will be of a different nature from that of parenchymatous tissue. Lymph and plasma infiltration and mast cells are the fundamental characteristics of the reaction caused by the spirochetes. Orton<sup>9</sup> says it is this association of plasma cells, then, in the perivascular spaces, and especially when they occur as a close-packed mosaic of angular forms around the smaller capillaries, the so-called "mantle infiltration," that forms the histological criterion, without which the diagnosis of paresis can scarcely be considered as established. Generally speaking, the spirochetes produce the same histological pathology as in other tissues. We find that paresis and tabes are anatomically just as cerebral and spinal, and the pathology is based in all cases on a similar reaction to the same agent. The reaction<sup>10</sup> to the injury of the spirochetes in the meninges is the proliferation of fibroblasts to replace those of adjoining fibroblasts which have been destroyed. The cortical cells are killed

<sup>7</sup> New York Med. Jour., August 29, 1914, p. 358.

<sup>8</sup> Jour. Exp. Med., February 1, 1913, xvii, p. 232.

<sup>9</sup> Am. Jour. Insanity, July, 1916, lxi, p. 91.

<sup>10</sup> Mallory: Principles of Pathological Histology, 1914.

slowly and diffusely here and there, and therefore the regeneration is diffuse. This reaction takes place slowly, as seen from the slow downward development of the case. The process in the meninges is chiefly confined to the bloodvessels, and they are filled with endothelial leukocytes which occlude the lumen, thereby causing necrosis, which is later replaced with calcium producing the cranial osteosclerosis, as found in 42 per cent. of the cases. These are evidently cases of long standing.

Quite a number of sections were made from several brains to demonstrate the presence of *Treponema pallidum*, with positive findings in only two sections. Levaditi's method was used. Noguchi,<sup>11</sup> in 1913, succeeded in finding the *Treponema pallidum* in 12 out of 70 specimens from the brains of paretics, and his findings were confirmed later by many observers. Foster<sup>12</sup> studied material from brain puncture from a series of 61 paretics by the dark-field illumination method and found active spirochetes in 27 cases (44 per cent.). Spirochetes have also been found in the cord and cerebrospinal fluid. These findings seem to prove Kraepelin's assertion: "We can today declare with the greatest certainty that syphilitic infection is necessary for the later appearance of paresis." Noguchi's discovery furnishes the fact hitherto wanting to complete the chain of evidence and demonstrates that paresis, as long held by Dunlap, is merely a late manifestation of syphilis, though presenting a somewhat different pathological picture from that seen in the hitherto recognized specific cerebral disorders which have been grouped by Nonne under three headings:

1. Syphilitic new growths.
2. Chronic hypoplasia inflammation.
3. Disease of the bloodvessels.

We can now add to the category paresis and tabes dorsalis, formerly the so-called parasymphilitic diseases.

Sections for microscopic study were taken from some of the brains and fixed in 10 per cent. formalin and some in Müller's fluid. The staining was done by Marchi's method for neuroglia, hematoxylin and eosin stains and concentrated aqueous solution of thionin. Sections were taken from the frontal, precentral and occipital cortex and infiltrated with paraffin and stained with the above methods. The findings in general were as follows: The nerve cells of the cortex were found to be in all stages of degeneration—shrinkage and disintegration. Many of the cells were absent. Some had lost the protoplasmic process and some the axon fibers. On account of the nerve cells being disarranged the normal layers of the cortex were confused and could not be made out. The tangential associa-

<sup>11</sup> Jour. Exp. Med., February 1, 1913, xvii, p. 232.

<sup>12</sup> Allg. Ztschr. f. d. Psychiat., Band lxxi, Heft 6.

tion fibers and collaterals were greatly reduced in proportion. As a result of this the cerebral convolutions were shrunken and fell apart and we have cerebral cortical atrophy, with widened sulci, as found in 54 per cent. of the cases.

Most of the brains examined have been hardened in formalin and were not sectioned until thoroughly hardened.

These 162 autopsies are among 1714 autopsies, thereby constituting 9.3 per cent. Among these 162 there were 124 males and 38 females. Out of the entire number there were only 9 negroes. The average age of death is forty-eight years, the male average being forty-nine years and the female average forty-three years. The oldest male case was sixty-two years and the youngest thirty years; the oldest female was sixty-one years and the youngest twenty-six years.

In the 162 cases of paresis the average weight of brain is 1190.5 grams, the lightest being 820 grams and the heaviest 1680 grams. The average weights of normal brains, according to race, were as follows:<sup>13</sup>

	Grams.
Caucasian . . . . .	1335
Chinese . . . . .	1332
Sandwich Island . . . . .	1303
Malay and Indian . . . . .	1266
Negro . . . . .	1244
Australian . . . . .	1185

The average English and American brain weighs 1346 grams.

The pathological findings in 162 cases of paresis and the percentage of each finding are summarized as follows:

	Per cent.
Chronic leptomeningitis . . . . .	100
Chronic pachymeningitis . . . . .	81
Hydrops meningeus . . . . .	72
Cranial ependymal sclerosis . . . . .	71
Dilated cerebral lateral ventricles . . . . .	60
Cerebral cortical atrophy . . . . .	54
Cerebral arteriosclerosis . . . . .	43
Cranial osteosclerosis . . . . .	42
Cystic choroid plexuses . . . . .	33
Chronic internal hemorrhagic pachymeningitis . . . . .	17
Pachycephalitis . . . . .	14
Cerebral softening and edema . . . . .	14
Cerebral congestion . . . . .	10
Chronic external and internal adhesive leptomeningitis . . . . .	8
Dilated fourth ventricle . . . . .	5
Coherent cerebral hemispheres . . . . .	4
Softening of velum interpositum . . . . .	3
Small thrombotic lenticular softenings . . . . .	3
Cerebral edema and softening . . . . .	2
Cystic and cheesy degeneration of choroid plexuses . . . . .	2
General cerebral atrophy and sclerosis . . . . .	2
Thrombotic softening of lenticular nucleus close to the posterior limb of the internal capsule . . . . .	2
Old area of thrombotic softening of both caudate nuclei . . . . .	2

<sup>13</sup> Emil Villiger's Brain and Spinal Cord, 1912, 3d ed.

### Findings appearing only once in the series are as follows:

Congested and thickened velum interpositum and softened pituitary body.  
Chronic adhesive pericranitis.  
Dilated third ventricle.  
Cerebral hemorrhage.  
Dilated cerebral perivascular lymph space.  
Cerebellar tumor.  
Thrombotic softening of right caudate nucleus and part of anterior and posterior limbs of the internal capsule.  
Calcification of falx cerebri.  
Small perivascular cerebral and cerebellar softenings.  
Tuberculoma of dura.  
Old hemorrhage of the right caudate nucleus.  
Thrombotic softening of the left putamen of the lenticular nucleus.  
Thrombosis of the right anastomotic vein of Trolaid.  
Cyst of the pia and arachnoid.  
Softening of the left cerebellar hemisphere involving the lobus semilunaris, lobus postero-inferior, lobus quadrangularis from thrombosis of the left vertebral and of the left postero-inferior cerebral arteries.  
Thrombotic softening of the posterior limb of the right internal capsule.  
Calcified nodules of the left temporal pole.  
Spindle-celled sarcoma of the right optic thalamus.  
Absence of middle commissure of optic thalamus.  
Small thrombotic cortical softenings of left cerebellum and right occipital lobes.  
Anomalous anterior cerebral arteries.  
Thrombosis of the right lateral and superior longitudinal sinus.  
Thrombotic softening of right lenticular nucleus and double optic atrophy.  
Thrombotic softening of the left cerebellar white tracts.

The microscopic findings were practically similar in the cases examined and consist of the following in general:

Syphilitic perivascular round and plasma cell exudate.  
Distortion of cerebral cortical layers.  
Chronic ganglia cell degenerative changes and cerebral gliosis.  
Acute and chronic degenerative ganglia cell changes with atrophy.  
Endarteritis and pericarditis.

A careful study of the pathological processes that have taken place in the brain of paretics will have an important bearing upon the treatment of syphilis. Quite a few men have reported improvement in cases of paresis with various forms of treatment. One goes so far as to make the remark that "I am still looking for *cures* in paresis." Cotton<sup>14</sup> gave antisyphilitic treatment to 66 cases of paresis, and his results were that out of the 66 he had 11 cases which he recorded as arrested and 7 much improved, but none cured. It will be recognized that antisyphilitic treatment can have no direct effects upon degenerating nerve structures, and therefore upon the symptoms and signs of paresis; nevertheless, it may prevent the occurrence of further reaction in other areas by killing the spirochetes. Even among the early cases of paresis which have been autopsied there is a considerable amount of nerve-cell destruction, and it is evident that there must be considerable damage to the brain before mental symptoms are apparent. In the advanced case the cell destruction is so marked that even if treatment could remove the spirochetes a large amount of mental defect would remain.

<sup>14</sup> Am. Jour. Insanity, July, 1915, lxxii, p. 150.

## REVIEWS

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**MEDICAL WAR MANUAL NO. 7. MILITARY SURGERY OF THE ZONE OF THE ADVANCE.** By **GEORGE DE TARNOWSKY**, Major, M. C., U. S. R., American Expeditionary Forces. Pp. 330; 36 illustrations. Philadelphia and New York: Lea & Febiger, 1918.

THIS small manual was prepared under the supervision of the Surgeon-General and the Council of National Defense for the guidance of medical officers working in the zone of the advance, and is remarkable for the amount of up-to-date necessary information confined within its covers. Its essential aim is to give a résumé of the primary treatment which has proved most satisfactory in the opinion of those best qualified to judge. Not only to those in actual service is it valuable, but to every physician who wishes to familiarize himself, with small effort, with the best the war has produced, on the Allied side, in the alleviation of the sick and wounded. Its description of the various activities of the medical man in the most interesting field of the war, the zone of the advance, may fairly be said to be fascinating.

T. T. T.

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**BIPP TREATMENT OF WAR WOUNDS.** By **RUTHERFORD MORISON**, Professor of Surgery, Durham University. Pp. 67; 9 illustrations. London: Henry Frowde and Hodder & Stoughton, 1918.

MORISON's contribution to the treatment of war wounds has been properly classed with the great discoveries in war surgery. It has been used widely, particularly by Englishmen, and the reported results have been very encouraging. This little book by the discoverer of the method describes it concisely and clearly and gives the various uses to which it has been applied with much credit to itself and the author. The name "bipp" was derived from the combination of the first letters of the name of each of its constituents, bismuth—iodoform—paraffin, with that of the word paste. The walls of the wound or abscess cavity having been cleaned thoroughly, a thin layer of the paste is smeared over the whole surface and the cavity closed completely by sutures, when possible, otherwise it is treated as an open wound.

T. T. T.

**"TRENCH FEVER." REPORT OF AMERICAN RED CROSS RESEARCH COMMITTEE. Oxford University Press, 1918.**

THE report is delivered in a 446-page, cloth-bound, super-royal octavo volume, well illustrated by charts and half-tones and plentifully interspersed with tables.

The commission consisted of Majors Richard P. Strong, Homer F. Swift and Eugene L. Opie and Captains Ward J. MacNeal, Walter Baetjer, A. M. Pappenheimer and A. D. Peacock. To these Lieutenant David Rappoport was subsequently attached. Of these officers all were Americans except Captain Peacock, and while much assistance was rendered by the British authorities in furnishing material and quarters, the work was conducted, with this exception, entirely by American agencies.

It appears as though the laboratory and other facilities were superior to those obtaining in many other lines of activity on the front, and this, coupled with the evident thorough organization of the personnel, has made possible the rich detail and preservation of minute records which are so refreshing to the scientific reader. One of the most impressive phases of the presentation is the able editing by Major Strong.

The research was directed particularly to the question of transmission because this phase was the most important in prevention, and so in conservation of man-power to the armies.

Points as to etiology are recorded only because they resulted from the main line of investigation.

Inasmuch as the disease is not transmissible to lower animals, American volunteers were used where such were necessary. Of these, 82 were selected out of several hundred offering themselves. In some respects the investigation parallels that of the Yellow Fever Commission of eighteen, and may well be considered as one of the finest pieces of American research conducted since that time.

*Clinical Features of Trench Fever.* These are particularly valuable from this source because they come from *known* cases of "pure-bred" trench fever, and the symptoms and signs, therefore, that are assigned to the disease cannot be questioned on the basis that they are those of some other P. U. O. (pyrexia of undetermined origin).

Prodromes was present in only two-thirds of the cases, consisting of headache generally one day before the onset; but in some cases headache and body pains antedated it by a week to ten days.

The onset is sudden, with more marked headache, chill and sudden temperature rise to 103° and 104°, great prostration and weakness. Most important in diagnosis is the tenderness which accompanies the frontal and postorbital headache, and the lumbar, thigh and calf pains. The spleen was not enlarged in 25 per cent. of the cases on the first day. A macular eruption similar to that of typhoid fever appears in 50 per cent. of the cases by the second day.

The course extended over a period of from one to several weeks, showing regular to irregular relapses of one or two days, with complete intermission of four or five days. The temperature rises suddenly to 103° or 104° in the exacerbations and suddenly drops in a day or two. Leukocytosis was found so variable as to offer no aid to diagnosis.

In short, the features common to many acute infections are present. "When trench fever assumes certain forms it is quite characteristic; when it assumes others it can only be diagnosed by taking all its positive features into consideration and by ruling out other diseases." And "In contradistinction to the ordinary infectious disease, trench fever is characterized by its tendency to relapse, by freedom from symptoms and signs between the relapses, in many cases by long persistence of the infection and in a few cases by distinct relapses, with long periods of apparent normality."

The need for laboratory aids in diagnosis is very evident in the doubtful cases and brings home to us what real advances have been made along these lines in the older and better-known infections.

The following conclusions were reached by the commission as the result of their experimental work.

1. That trench fever is a specific infectious disease; that it is not a modified form of typhoid or paratyphoid fever and is not related from an etiological standpoint to these diseases.

2. That the organism causing the disease is a resistant filterable virus.

3. That the virus causing trench fever is present particularly in the plasma of the blood of trench fever cases, and that such plasma will produce the disease on inoculation into healthy individuals.

4. That the disease is transmitted naturally by the louse (*Pediculus humanus*, Linn., var. *corporis*), and that this is the important and common means of transmission. That the louse may transmit the disease by its bite alone, the usual manner of infection, or the disease may be produced artificially by scarifying the skin and rubbing in a small amount of the infected louse excrement.

5. That a man may be entirely free from lice at the time he develops trench fever, the louse that infected him having left some time previously as its host, and that the louse need only remain upon the individual for a short time in order to infect him.

6. That the virus of trench fever is also sometimes present in the urine of trench fever cases and occasionally in the sputum, and that the disease may be produced in man by the introduction of the virus in the urine or sputum through the scarified or otherwise abraded skin.

7. That since the urine and sometimes the sputum of trench fever patients are infective, these should be sterilized in order to avoid the possibility of accidental infection from them.

8. That in order to prevent trench fever or limit its spread, and



thus save man-power for the armies, greater efforts must be made to keep soldiers in general from infestation with lice.

The above conclusions were reached on the basis of the following (among other) findings:

Blood from trench fever cases inoculated into mice, white rats and guinea-pigs yielded no typhoid organisms in the animal.

Blood, urine and feces cultures from trench fever cases at different stages of the disease resulted negatively for the typhoid group of organisms.

The agglutination titer in trench fever (after the method of Dreyer) did not correspond to that of a typhoid group infection following antityphoid vaccination.

The virus resists 60° C. moist heat for thirty minutes, but is killed by 70° C. moist heat for thirty minutes.

The virus is not killed by drying (urine, louse excrement).

Trench fever urine filtrate (Chamberland L. unglazed porcelain) produced the disease in one out of two volunteers inoculated.

Saline suspension of louse feces similarly filtered produced the disease in two out of three men inoculated.

Twenty-three men out of thirty-four inoculated intravenously with trench fever *plasma* contracted trench fever. Whole blood and clear unfiltered plasma contained most of the virus (23 out of 25 trials; washed erythrocytes little or none, 4 trials).

The virus is therefore probably not intracellular.

Filtered plasma was not infectious, probably on account of the colloid of the serum obstructing the pores of the filter (6 trials).

The incubation period varied between five and twenty days, depending on the stage of the disease at which the blood was taken.

In testing the following louse transmissions, thirty-eight men were used.

Twenty out of twenty-six men artificially infested with trench fever lice developed trench fever.

Five men out of five tested were infected by the *bite* alone.

Eight men were infected by scarifying the skin and rubbing in trench fever louse excrement.

In the above louse experiments it was found that lice may remain infective for *at least* thirteen days.

The inoculation period in louse-bitten cases is from fifteen to thirty-eight days, with an average of twenty-one days.

Two men bitten by hundreds (1500) of offspring of trench fever lice did not contract the disease. That is, the virus is not hereditary in the louse. The commission evidently inclines to the belief, without so stating definitely, that the virus has a life-cycle in the louse. This is suggested by the longer incubation period of trench fever by *louse* transmission than by direct *blood* inoculation, but the committee guards its opinion by granting that the longer period could also be explained by the smaller amount of virus inoculated. To

this the reviewer would add that the virus might also be biologically modified by its habitat in the louse in such a way (reduction of virulence) that it would take the longer time to produce the onset of the disease, and that certainly the louse is not an obligate intermediate host at all stages of its life-cycle (if it has one), as shown by successful direct blood transmission.

Conclusion No. 7 is important in regard to camp sanitation. Because the subject carries no lice and appears healthy is no reason why he may not be in the incubative stage of the disease.

Attempts to infect with trench fever *feces* failed (three trials).

One man out of three was infected by rubbing trench fever sputum into scarified skin.

Five out of eight were infected by dried (one week) urinary sediment from trench fever cases.

The war is now over and the research loses, with it, much of its surface glamor and does not urge upon us as it would have done a year ago. But it has rendered services which are permanent. It has established, first, the series of facts enumerated above regarding the titular subject, trench fever. In the second place it has further incriminated the already convicted louse and indicates that here we may expectantly inquire for a few (or more) other morbid potentialities in this parasite which the world war did not bring out. In the third place it shows that systematic, correlated, refined, properly controlled and minutely reported research *can* be done (in spite of field difficulties) when systematically prearranged by some central organization like the American Red Cross, Public Health Service or like body. And, finally, we find that when the occasion arose there were, like Doctors Lazear, Carroll and other members of the Yellow Fever Commission, eighty-two American citizens ready to submit themselves to inoculation with a disease of unknown causation for the merely possible and unguaranteed benefit of their comrades-in-arms. W.

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WAR WOUNDS OF THE LUNG. By PIERRE DUVAL, Chief Surgeon of Mobile Unit No. 21, of the French Army. Pp. 99; 27 illustrations. New York: William Wood & Co., 1918.

THE recent war has been responsible for many valuable contributions to surgery, but very few have been more brilliant than those on the treatment of war wounds of the lungs, and of these none have been more revolutionary than the contributions of Duval. Early in the war he took the position that the let-alone treatment of lung wounds with grave complications, so generally followed at that time, should not prevail. He insisted that direct exposure, cleansing and suture of the wounds would save many cases that were then

dying. Since then his views have been widely accepted by the profession. This small volume is an epitome of his war work on the lung, and should be in the possession of every surgeon who would become familiar with the progress of lung surgery. When we recall how slowly and laboriously were developed the low-pressure chambers and high-pressure apparatus to prevent the supposedly dangerous collapse of the lung when the pleural cavity was opened, we realize how revolutionary was the surgeon who dared to open the chest widely without such aids, deliberately permit the lung to collapse, bring it out through the wound for inspection and manipulation, trim the ragged, devitalized wound surfaces, cleanse them and close the lung wound by sutures as any other wound, and after cleansing the pleural cavity replace the repaired lung within the thoracic cavity and hermetically close the chest wound. This brilliant conception carried through with great courage has met with remarkable success.

T. T. T.

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SURGICAL CLINICS OF CHICAGO. By NUMEROUS AUTHORS. Volume II, No. 3, June, 1918. Pp. 254; 63 illustrations. Philadelphia and London: W. B. Saunders Company, 1918.

URINARY calculi are discussed by Albert J. Ochsner, Kolischer and Eisenstaedt and gall-stones by Ochsner, Bevan and Smithies. The latter contributes an interesting study of 1000 cases of gall-stone bladder disease. Eisendrath's presentation of five cases of injuries of the thorax and his discussion of the progress made during the war in the surgery of the chest are very valuable, as are all the articles in this number of the *Surgical Clinics*.

T. T. T.

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MANUAL OF SPLINTS AND APPLIANCES FOR THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY. By Lieutenant-Colonel W. L. KELLER, M. C.; Major R. B. OSGOOD, M. R. C.; Major A. LAMBERT, M. R. C.; Major J. A. BLAKE, M. R. C.; Captain W. S. BAER, M. R. C., and N. ALLISON, M. R. C., Members of a Board Appointed for the Standardization of Surgical Appliances. Pp. 173; 43 illustrations. New York: Oxford University Press.

THE character of the contents of this very brief manual may be judged by its title and by the names of its authors. The splints and appliances were adopted because of their efficiency and correct mechanical principles, simplicity of design, low cost of construction and transportability. It is largely illustrative, with a brief general consideration of the whole subject and detailed description of the splints and appliances of the surgical dressings and accessory supplies.

T. T. T.

**AMPUTATION STUMPS: THEIR CARE AND AFTER-TREATMENT.** By G. MARTIN HUGGINS, Medical Officer to the Government Schools. Pp. 21; 95 illustrations. London: Henry Frowde and Hodder & Stoughton, 1918.

THE author aims to supply a guide to the large number of surgeons engaged in treating cases in which amputation has been performed. There is great need of it because of the new amputation wound conditions resulting from the war. For example, the very severe wound infections characteristic of this war have led to more and more frequent employment of the guillotine amputations, by which term is meant all flapless, more or less circular amputations that are left open and unsutured to save life because of the presence of virulent sepsis. The fitting and selecting of suitable artificial limbs and appliances for various occupations receive much attention in the text and illustrations. The same is true of the complications frequently arising in connection with amputation stumps. T. T. T.

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**ESSENTIALS OF MATERIA MEDICA AND THERAPEUTICS (LIPPINCOTT'S NURSING MANUALS).** By JOHN FOOTE, M.D., Associate Professor of Therapeutics, Georgetown University School of Medicine. Pp. 310. Philadelphia: J. B. Lippincott Company, 1918.

THE present edition is the third of this useful book for nurses. The number of remedies considered is purposely limited for simplicity and the principal classification is according to physiological action. The subject-matter is clearly written and with sufficient detail. The reviewer is familiar with no text-book that better suits the needs of nurses. Some little criticism may be made regarding the appended formulas, in view of the fact that nurses are so frequently tempted to prescribe, oftentimes to the discredit of medicine. The attempt to outline rules and formulas for infant feeding in two pages is poorly done. C. N. S.

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**MEDICAL CLINICS OF NORTH AMERICA,** March, 1918. Volume I, Chicago Number. Philadelphia and London: W. B. Saunders Company, 1918.

IT is an appreciated opportunity to be taken with each issue of this publication to the clinics of well-known authorities to grasp their methods of analysis and to learn of their views on subjects of such general interest. The present volume takes us to the clinics

of Chicago. Dr. Charles Louis Mix has us consider some of the fundamental principles underlying the diagnosis of the more usual cardiac diseases. Dr. Solomon Strouse presents juvenile diabetes in twins; a case illustrating the Karrell treatment of edema and two cases showing the importance of details in the treatment of angina pectoris. Dr. Charles A. Elliott discusses the radium treatment of leukemia and presents one case with splenectomy. Dr. Frederick Tice refers briefly to epidemic respiratory infections. Dr. Charles Spencer Williamson presents a case of polycythemia. Dr. Milton Portis analyzes the differential diagnosis of lesions of the right upper quadrant of the abdomen, as evidenced by 8 cases. Dr. Arthur Elliott describes syphilis of the aorta; Dr. Joseph Freidman considers reflex gastric disturbance; Dr. Julius Hess, tuberculin skin reaction in childhood; Dr. Frank Wright, nephritis; Dr. Arthur Byfield, splenomegaly and cirrhosis of the liver; Dr. Ralph Hamill, insomnia and hysteria; Dr. Isaac Abt, asthma in children; Dr. Maximilian J. Hubeny, roentgen examination of the appendix; Dr. Henry Helmholtz, pyelitis in the newborn. C. N. S.

PROTEOMORPHIC THEORY AND THE NEW MEDICINE. By HENRY SMITH WILLIAMS, B.Sc., M.D., LL.D. Pp. 304. Goodhue Company, 1918.

NEW theories and new applications of old theories are earnestly sought after by the medical profession, facing, as it does, problems pertaining to the cure of diseases that still await solution. The reviewer is, however, in doubt as to a suitable analysis of this work. It is certainly not presented after the fashion of our usual scientific treatises and undue emphasis is too frequently made to the originality of the author.

The study of proteins and anaphylaxis have, however, opened new viewpoints that bear on diagnosis and treatment of disease. The experiences, therefore, of any worker in this field may throw some light. Reference in this volume is made principally to the use of vegetable proteins, the author considering the proteins from alfalfa meal, alfalfa seeds and millet seeds most satisfactory. The injection of these proteins hypodermically in cancer subjects is claimed to alleviate pain, modify the discharge, modify the tumor itself and favorably influence the general health and mental attitude of the patients. The same proteins are observed to benefit markedly cases of (a) rheumatoid arthritis; (b) pulmonary tuberculosis; (c) pernicious anemia; (d) intestinal toxemia; (e) leukemia; (f) Graves's disease; (g) psoriasis; (h) asthma; (i) arteriosclerosis; (j) neurasthenia; (k) primary and secondary anemias.

The first part of the book is taken up with the theories involved, the blood changes noted and the mechanism of protein hydrolysis and immunization. The second part of the book has to do with observations as to the benefit derived from protein therapy. Unfortunately, what truths may be contained in its pages lose much of their appeal because of the manner of presentation. C. N. S.

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INTERNATIONAL MEDICAL ANNUAL. A YEAR-BOOK OF TREATMENT AND PRACTITIONERS' INDEX. Thirty-sixth year. Pp. 666. New York: William Wood & Company, 1918.

THE reviewer has appreciated in previous years the merits of this synopsis of medical progress, and unhesitatingly commends this present edition as even surpassing the others in scope and selection of material. As a review of practical medical progress it is extremely useful, being easy of reference and adequately complete in detail.

In the present volume special emphasis is placed on the dictionary of remedies and treatment, including radioactivity and electrotherapeutics. Naturally, war injuries and war diseases are considered fully. The reviews are from as world-wide sources as the present medical literature permits. The wonder is that the contributors have been able to do as much as they have under the wartime conditions existing. C. N. S.

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AIDS TO RATIONAL THERAPEUTICS. By RALPH WINNINGTON LEFTWICH, M. R. C. S., Eng. Pp. 233. New York: William Wood & Company, 1918.

A VOLUME small in size yet large when measured by the number of practical therapeutic suggestions filling its pages. A physician in the toils of a general practice appreciates in a book on therapeutics an author's clear-cut expression of his views and methods proved to his (the author's) satisfaction by actual experience. Such methods and views are here described, and while now and then they will run counter to the experiences of the reader, interpreted as they are meant, they will prove of great value.

Disregarding the time-honored custom of considering therapeutics in connection with diseases, classified according to the organs affected, he places in the same group all diseases which are of allied pathology and which require the same treatment. This undoubtedly avoids much repetition and impresses the essentials of group treatment, but for reference necessitates the use of the index, for certain diseases are properly considered under several various groups

according to the stage of the disease. There is more to be said in favor of the plan for the reviewing of therapeutics by general practitioners with experience back of them than for teaching therapeutics to under-graduates.

To give some idea of the manner in which the groupings are made a few of the forty-two chapters may be mentioned. He refers to the automatic habit group, the catarrhal group, the abscess group, the hemorrhagic group, the infective fever group, the intracranial pressure group, the colic group, etc.

His manner of therapy is indeed rational and thoroughly up-to-date, at least as much so as any one man can be in so many lines. He pleads for more extensive medical therapy used, with judgment, and favors many of the old measures that have been so thoroughly tested yet seem to be now discarded. He disputes the ground the surgeons take in considering appendicitis that all should come to operation.

The book is of no scientific value but would be a help to any general practitioner, though unfortunately many of the prescriptions contain drugs that are but slightly used in this country.

C. N. S.

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GENITO-URINARY DISEASES AND SYPHILIS. By HENRY H. MORTON, M.D., Clinical Professor of Genito-urinary Diseases in the Long Island College Hospital. Fourth edition. Pp. 807; 330 illustrations and 36 full-page colored plates. St. Louis: C. V. Mosby Company, 1918.

THE fourth edition, revised and enlarged, of Morton's *Genito-urinary Diseases and Syphilis* from the press of a new publisher is a most commendable achievement and the work is destined to be a monument to the sterling judgment of the author. A careful review of the book evokes commendation for each chapter, and there exists little to criticise. The first forty chapters are devoted to the various diseases of the urological and genital tracts, including radiography, pyelography, cystoscopy, urethroscopy and tests of kidney function. It is noted that many of the cystoscopic and urethroscopic views are borrowed from other authors. Chapter XLI deals with chancroid and its complications. The wisdom of omission of the high-frequency and copper sulphate treatment of this disease might be questionable. Chapter XLII presents a consideration of erosive and gangrenous balanitis, the so-called fourth venereal disease. The remaining ten chapters are devoted to syphilis and are most commendable, the author concisely systematizing the subject and presenting the important points in a lucid and impressive manner.

So excellent are the chapters on chronic urethritis, prostatitis, seminal vesiculitis, urethral stricture, tumors of the bladder, urinary calculus, prostatic enlargement and diseases of the kidneys that minor criticisms appear ill-advised if not out of place. Nevertheless, the reviewer regards it as his duty to take exception to certain statements relative to the application and utility of indigocarmine as a functional kidney test, believing that its applicability is just as great in other diseases and conditions as in renal tuberculosis, in which particular disease its employment obviates the necessity of catheterization of the presumably normal ureter and kidney, a procedure not unattended with danger. He also disapproves of any illustration or description of Luy's segregation in a modern textbook on genito-urinary surgery. Exception might also be taken to the space devoted to the treatment of glandular hypospadias in comparison with that given to the penile and perineal forms of the malformation. It is unfortunate that more consideration is not given to the disposition of the uterus in nephrectomy for tuberculosis. It is observed that no mention is made of teratoma testis. The reviewer has had no personal experience with Ultzmann's brush apparatus in the treatment of old foci of inflammation in urethritis, but he deprecates the value of "sealing in" treatment to abort gonorrhea, astringent injections and the use of gonosan as an internal remedy superior to other substances commonly employed and less expensive. Due credit is due the publisher for the excellence of the illustrations and the type employed in this edition. B. A. T.

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THE PREVENTION OF VENEREAL DISEASES. By OTTO MAY, A.M. (Cantab.), M. R. C. P., London; late Hon. Secretary National Council for Combating Venereal Diseases. Pp. 240. London: Oxford University Press and Hodder & Stoughton, 1918.

THIS timely topic is broadly dealt with by May from the standpoint of preventive medicine, the author particularly emphasizing the proved value of the application of local measures of prophylaxis or early treatment in the prevention or abortion of gonorrhea and syphilis. The importance of education in biology and the physiology of reproduction is regarded as a valuable aid in the elimination of venereal diseases, but its futility is recognized. Legislation aiming at the control of prostitution and vice has been and is still a recognized failure in the control of venereal diseases. The author justly concludes that personal prophylaxis or early treatment with the recognized drugs will accomplish more than other means in the prevention of venereal infections. W. H. M.



# PROGRESS OF MEDICAL SCIENCE

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## THERAPEUTICS

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UNDER THE CHARGE OF

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**Prophylactic Value of Leary's Vaccine.**—BARNES (*Jour. Am. Med. Assn.*, 1918, lxxi, 1899) describes the epidemic of influenza which developed at Wallum Lake, R. I. Of the population (225 patients and 94 employees) 25 per cent. were affected. Of the 114 young adults who were exposed to the disease, 40 per cent. developed influenza; 172 employees and patients were injected with prophylactic doses of an influenza vaccine furnished by Dr. Timothy Leary. However, the incidence of influenza was 20 per cent. among both the vaccinated and the unvaccinated. In 25 influenza cases following vaccination, 4 cases, or 16 per cent., died, and in 57 cases of influenza among the unvaccinated the mortality was 9, or 15.8 per cent. The conclusions drawn are that the morbidity was only slightly lower among the vaccinated and that the mortality among those developing influenza was practically the same whether vaccinated or not.

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**Experimental Study of Serum Therapy in Trichinosis.**—From experiments on rats, HALL and WIGDOR (*Arch. Int. Med.*, 1918, xxii, 601) conclude that serum from animals convalescent from trichinosis when injected into other animals or fed to them mixed with trichinous meat does not prevent the development of trichinae. However, the longevity data from these experiments, the clinical observations of Salzer, as well as theoretic considerations, lead them to believe that such a serum may be of decided value in combating the toxic features of trichinosis.

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**Effects of the Injections of Epinephrin in Soldiers with Irritable Heart.**—PEABODY (*Jour. Am. Med. Assn.*, 1918, lxxi, 1912) and others have tested the effect of the injection of 0.5 c.c. of a 1 to 1000 solution of epinephrin in normal soldiers and in soldiers suffering from "irritable heart." In only one of the 27 control cases was there a suggestion of hypersusceptibility to epinephrin. In 65 patients the epinephrin

test was positive in 39, doubtful in 6 and negative in 19. The most important symptoms of the reaction were the presence of tremors, sweating, flushing, pulsation of peripheral bloodvessels, general nervousness and increase in blood-pressure, pulse-rate and depth of respiration. Furthermore, the "irritable heart" cases showed an increase in basal metabolism and in blood sugar more marked than in normal individuals. The electrocardiogram showed most constantly a slight decrease of the height of the *T*-wave. In individual cases other abnormalities were seen, such as increase of sinus arrhythmia, prolongation of *P-R* interval, partial heart-block, inversion of the *T*-wave and the production of ventricular extrasystoles. Peabody advises the use of epinephrin as an aid in the diagnosis of "irritable heart."

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**Contributions to the Physiology of the Stomach; Studies on the Control of Hunger by Drugs.**—In this paper, GINSBURG and TUMPOWSKY (*Arch. Int. Med.*, 1918, xxii, 553) report the results of an investigation into the action of drugs on the hunger mechanism. Gastric fistulæ were produced in twelve dogs, and in four of these both vagi and splanchnics were cut ("isolated" stomachs). The drugs were usually administered subcutaneously in therapeutic doses. Atropin was found to inhibit gastric activity, counteracting the effect of pilocarpin and eserine (both of which increased the movements of the stomach, while the pulse-rate was coincidentally diminished). Cocain caused a profound and lasting inhibition of gastric movements, which seemed less marked in the "isolated" stomachs. Camphorated oil was without effect when given subcutaneously; when administered intramuscularly a prolonged increase in activity was observed. Strychnin, in doses of  $\frac{1}{80}$  to  $\frac{1}{40}$  grain subcutaneously, increased gastric tonus, and at the same time there appeared to be a definite increase in the hunger contractions themselves. Direct application to Auerbach's ganglia also caused stimulation. The inhalation of 5-minim pearls of amyl nitrite caused only temporary inhibition of contractions; in animals with sectioned splanchnics and vagi, in addition to inhibition the tonus remained depressed for a long time, only gradually returning to its original level. Epinephrin intravenously caused a prompt and marked inhibition of the hunger contractions, lasting from one to two hours. Absorption from the raw surface of the fistula caused equally profound depression, but application to the nasal mucosa was without effect. Pituitrin is supposed to stimulate smooth muscle, regardless of its innervation, but in these experiments its action was remarkably like that of epinephrin, inhibition occurring immediately after subcutaneous injection. The duration of the effect, however, was much less. Other observers have noted that pituitary extracts may inhibit the movements and tonus of isolated intestinal loops. Ergot, administered intravenously, was usually followed by temporary inhibition of the gastric contractions, followed by lowered tonus and the resumption of the contractions. Intramuscular injection in one instance gave a tremendous step-like rise, with extremely high tonus, followed by a short rest and then another active period. No differences were noted in the response of the "isolated" and "intact" stomachs, except in the case of cocain, in which the action was less marked on the "isolated" stomach.

**OBSTETRICS**

UNDER THE CHARGE OF

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**Rupture of the Uterus through the Cesarean Section Scar.**—NOVAK (*Jour. Am. Med. Assn.*, July 13, 1918) states that in 1913 there had been reported 63 cases of rupture of the uterus through a Cesarean section scar. In 1916 this had increased to 74, and others have been reported. His own case is as follows: A white woman, aged nineteen years, had a Cesarean section May 5, 1916, for eclampsia; the child was dead but the mother recovered, with a slight infection of the abdominal incision. The second pregnancy was normal in every way, the last menstruation having been the end of August, 1917; the patient went into labor and was sent to the hospital, where she stated that she had but a few typical labor pains, when these were followed by severe and constant pain over the entire abdomen, with rigidity of the abdominal wall. This persisted for three days, with fever and slight increased pulse. At about the fourth day the patient felt better and remained in the hospital awaiting active labor. No fetal heart sounds were heard after the abdominal pain, nor did the patient perceive fetal movements. About six weeks after the expected time of confinement the patient was examined, when the abdomen was enlarged to the size of a full-term pregnancy. The walls were so rigid that the fetus could not be palpated; there were no heart sounds. On vaginal examination no presenting part could be felt. The cervix was closed and firm, not resembling that of pregnancy. But one diagnosis seemed possible in the case, rupture of the uterus through the scar, with escape of the fetus into the abdominal cavity. At operation a thick spongy tissue was found just above the umbilicus, which proved to be a placenta. The amniotic sac was opened just above the placental area and about 2 quarts of amniotic fluid escaped. A large partly-macerated fetus was found lying obliquely in the abdominal cavity, the head above and to the right under the diaphragm, the extremities extending downward to the left. The amniotic sac was intact except where it had been incised on opening of the abdomen. After rupture of the uterus it had undergone involution, being about the size one would expect six weeks after labor. Through the line of the old incision the uterus had split asunder, extending from the fundus to about the level of the internal os. The placenta had been turned out through this opening, partly reimplanting itself later on the anterior parietal peritoneum. Both Fallopian tubes were covered with light adhesions and the right ovary was cystic, about the size of a small hen's egg. A subtotal hysterectomy was performed, the left ovary, which was normal, being saved. On removing the body of the uterus, with the tube, placenta, umbilical cord and fetus, a very large cavity was left. The inside of this was lined by tightly adherent amniotic membrane, which was removed where this was possible. The large cavity was treated by

placing several good-sized cigarette drains in various portions, bringing them out through the abdominal incision. The wound was closed in tiers, reinforced by interrupted silkworm sutures. The recovery from the operation was uneventful, the patient being discharged from the hospital three weeks after its performance. It was interesting to note in this case that although the uterus was ruptured there was no internal hemorrhage or shock. This has been seen by other observers. It is possible that the pressure of the child's head through the rent may have something to do with the prevention of the hemorrhage. There were no signs of old or recent hemorrhage, nor was there to any appreciable degree shock at the occurrence of the rupture. The occurrence of infection of the abdominal incision with fever for several days after Cesarean section in 1916 is very significant, and according to our knowledge of the causes of rupture of the scar this gives ample explanation for its occurrence in this case; the invasion of the uterine scar by decidual elements is thought by some to be an important factor.

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**Delivery by Abdominal Section.**—DAVIS (*Am. Jour. Obst.*, May, 1918, reviews the conditions which are today admitted to be valid indications for delivery by abdominal section. He states that at present delivery through the vagina is limited to those cases in which a living child can thus safely be born with minimum injury to the mother. Great disproportion between mother and child with living child, accidental separation of the normal placenta, rupture of the uterus, ectopic gestation, a history of previous labor, with unusual difficulty with fetal mortality and maternal morbidity, and the presence of foreign growths making vaginal delivery impossible, give a clear indication for delivery by abdominal section. Placenta previa and prolapsus of the cord in primiparous patients, with partly dilated cervix and cases of eclampsia, where the birth canal is undilated and unyielding, are said by him to be valid reasons for delivery by section. The advantage of elective section at a time and under circumstances most favorable to patient and physician is set forth. The advantage of the classic section and the fact that it enables the operator to close the uterus most efficiently, thereby preventing subsequent rupture of the scar, are stated. Cesarean section for a peritoneal fistula is stated to give good results in the hands of those skilled in its employment, but it is not yet practised by the majority of American obstetricians. Should the indication be present to sterilize the patient the advantages of hysterectomy, with the removal of the tubes and ovaries and often the appendix, are considered sufficiently great to commend this operation. When delivery must be performed in septic cases the rule should be observed that the uterus should be extirpated or that the uterine stump should be left outside the peritoneal cavity. Delivery by abdominal section is undoubtedly the safest method of birth for the infant. The statement is made that the operation is not unnecessarily performed, and to illustrate this the records of 51 hospitals in one city are cited. In these in one year there were 78,905 operations described as surgical, 6498 operations called gynecological and 862 under miscellaneous headings (operations of the nose, throat, eye and ear), giving a total of 86,255 operations. During the same year in these hospitals there were performed 114 deliveries by

abdominal section. This would scarcely indicate that delivery by abdominal section is too frequently performed. The writer states that up to the time of writing his cases of delivery by abdominal section which were uninfected and in fairly good condition at the time of operation numbered 194, with a maternal mortality-rate of 1 per cent., and cases infected and in bad condition when delivered numbered 66, with a maternal mortality-rate of 30 per cent. The general mortality-rate was approximately 8 per cent., which compares favorably with other major surgical operations performed upon a similar number of cases varying in all degrees of preparation, absence of preparation and complicated and uncomplicated conditions.

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**Can the Frequency of Some Obstetrical Operations be Diminished?**  
—VOORHEES (*Am. Jour. Obst.*, June, 1918) reviews the conditions pertaining in obstetric practice some years ago and draws attention to the fact that the high application of forceps and version are considered operations of very uncertain result and avoided if possible; craniotomy is rarely performed. Eclampsia has become much less frequent than formerly. The number of patients delivered in the hospital is greatly increased and there are more physicians who are specialists in obstetrics and there has been a general improvement in obstetric education. He believes, however, that there is still much indifference, ignorance and bungling work among the rank and file of the medical profession who practice obstetrics, and even obstetricians are guilty of mistakes and errors. One of the crying needs is for more faithful attention to pregnant patients to prevent toxemia; urine examinations should be frequently made and thoroughly done and a careful physical survey of the patient should be thoroughly conducted. A nitrogen partition in the urine should be made whenever indicated. If traces of albumin are found, a daily examination should be made. While it is true that acute fulminant toxemia may suddenly destroy a pregnant patient, most cases have premonitory symptoms, which call attention to the necessity for treatment, and if the patient does not respond to such treatment pregnancy must be interrupted. The writer states that in his private practice he has had but one case of eclampsia; before labor this patient did not obey directions, nor were specimens sent regularly. To illustrate the fact that eclampsia is becoming less he quotes the statistics of the Sloan Hospital; these show that from January 1, 1901, to December 31, 1905, inclusive, there were 113 cases of eclampsia in 7145 deliveries, or 1.5 per cent. From January 1, 1911, to December 31, 1915, there were 74 cases of eclampsia in 9224 deliveries, or 0.8 per cent. These statistics would indicate that more patients consult their physicians early in pregnancy and that the patients have better care. He calls attention to the value of correcting by external manipulations abnormal presentations. In the first 200 cases which the writer delivered there were ten breech presentations, while in the last 200 cases there were but six deliveries with that presentation. The writer admits that it may be impossible to change a breech to a head presentation in a primipara where the fetal legs are extended and this is especially difficult if there is a scanty amount of amniotic liquid. It is also possible in many cases to change a brow or face presentation to a vertex. In

all cases where there has been the production, in former pregnancies, of an unusually large child, measures should be taken to limit the development of the fetus in any subsequent pregnancies. This may be done conveniently by limiting the amount of carbohydrates which the woman takes after the sixth month. He calls attention to a case in which the patient had borne a first child successfully; in subsequent pregnancies there was great difficulty because the shoulders were largely developed and could only be delivered by extreme traction resulting in the loss of the child. In the third confinement a very strict diet was followed, with the result that a well-developed and nourished child was born spontaneously. In another case the induction of labor completed the care during pregnancy. To limit the over-development of a child he believes long walks during pregnancy are exceedingly valuable and also the wearing of a carefully-fitted corset. He draws attention to the success of Cesarean section in contracted pelvis; a very careful measurement of the pelvis will show that in the essential diameters there is considerable room; where however there is evident disproportion of a marked nature, then Cesarean section, often elective, gives good results. Regarding pituitrin, the conditions present for its safe employment are as follows: The cervix must be completely dilated and effaced and the membranes ruptured, the presentation normal and there must be proper relation between the fetal head and the maternal pelvis throughout. The writer has little confidence in the so-called "twilight sleep" method, but has found that nitrous oxide and oxygen are sometimes beneficial; if used too long and too frequently there is a distinct tendency to postpartum hemorrhage. The writer has faith in the efficacy of quinin and castor oil to bring on labor and in the action of a dilating bag introduced one or two weeks before full term. The statistics of the Sloan Hospital show that the use of forceps and the induction of labor are less frequently employed than formerly, but there seems to be an increase in the high forceps operation, which the writer says is surprising. Craniotomy is much less frequent; symphysiotomy and pubiotomy have been practically abandoned. Cesarean section has become much more common. He states the case of a primipara, aged thirty-six years, from whom had been removed the appendix and gall-stones. There was more or less abdominal pain and discomfort during pregnancy and the patient stated that she could not walk. Pelvic measurements were normal; the child was in breech presentation; this was changed to a vertex. An attempt to bring on labor by castor oil and quinin was made, but this failed; when labor developed it was delayed by an unusually firm cervix and a bag was introduced and later high forceps operation was performed. The child died as a result of pressure. The cervix was considerably torn and the mother made a tedious recovery complicated by phlebitis. The writer also states the case of a woman, aged thirty-eight years, in whom the fetus died from some unknown cause during pregnancy and after giving birth to several children; she lost several pregnancies by abortion and death of the fetus. This produced a condition of mental depression. Her last conception occurred when she was forty-four years old and the patient was carried on to within three weeks of term, when an elective section was done which resulted successfully. In this case the Wassermann reaction was always negative and no definite cause could be found for the death of

several of the children during pregnancy. The indication is that Cesarean section is frequently performed, and when the operation is chosen with good judgment the results are exceedingly good. It must, however, be remembered that in each case an operation is to be avoided rather than chosen and that very often ordinary measures, patiently and skillfully applied, are successful. It seems to the reviewer that while many obstetric operations are less frequently performed, there is a special need for skill and knowledge in obstetrics and for the exercise of good judgment. The success of Cesarean section impels many physicians and surgeons to undertake it who have not had experience to choose it wisely nor training to perform it properly. Good judgment is required to know upon what indication to induce labor, and no greater mistake can be made than the indiscriminate induction of labor. The management of pregnancy is most important as regards the labor which awaits the patient, and much can be done in this way to obviate dangerous and difficult procedures. The most hopeful sign in obstetric work is the fact that obstetrics is recognized as an important and distinct specialty for which special and thorough training is necessary, and which embraces a wide and important field in pathology and operative surgery. While certain operations may be less frequent, the demand for skill, experience and judgment is greater than ever before.

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#### **Sensitized Vaccines in the Prophylaxis and Treatment of Infections.**

—CECIL has contributed an extremely interesting paper upon this subject, giving a table of cases and the totals of his observations. His experience includes 20 cases in which sensitized typhoid vaccine was employed, 16 cases in which a sensitized gonococcus vaccine was used, 5 in which a sensitized streptococcus vaccine was employed and 1 case in which he employed sensitized *Staphylococcus aureus*; 4 cases of tuberculous adenitis and in 1 case of Pott's disease he used sensitized tuberculin. He finds that a vaccine sensitized with a homologous serum produces less disturbance when injected subcutaneously than does non-sensitized vaccine. In his series of 47 cases in typhoid it was found that the sensitized vaccine gave less reaction than the ordinary typhoid vaccine; as this may indicate that its protective power is less, it would not be advisable to substitute it at present for the ordinary vaccine. So far as the results obtained were concerned the sensitized vaccines gave no better effect than the ordinary vaccine. There were a few cases of recovery after treatment where ordinary vaccines had failed, but this may have been because a larger dose was used, which was made possible by the lessened disturbance produced by the sensitized vaccine. The chief objection to their use lies in the increased labor and time required in their production, and it would seem advisable to limit their use to those infections in which there is unusual sensitiveness to the ordinary vaccine or in which the ordinary vaccine had failed. While the writer does not mention puerperal septic infection, his cases include two patients suffering from gonorrheal vaginitis and one case of gonorrheal urethritis during the pregnant condition.

## GYNECOLOGY

UNDER THE CHARGE OF

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**Estimate of Radium Therapy in Uterine Cancer.**—STONE (*Am. Jour. Obst.*, 1918, lxxvii, 390) has recently made a report on the estimated value of radium therapy in uterine cancer, based on a study of 400 cases treated at the Memorial Hospital in New York, 80 additional cases being under observation at the time of the report. Radium, they have found, is an agent more peculiarly suitable for the arrest of the progress of the disease than any other method that has been hitherto employed, being more effective in primary lesions than in recurrences. New patients are kept in the hospital three, four or more days in order that the medical records, physical examinations and laboratory tests may be made and sufficient time allowed to recover from the nausea and slight malaise which the application of radium may cause. For purposes of classification the cases are divided into (1) extremely advanced, (2) advanced, (3) borderline and (4) early. Extremely advanced lesions include those in which all the pelvic structures appear to be palpably involved, forming either bulky tumors in the upper part of the pelvis, and often extending far down into the septa between the vagina and rectum or bladder, or a large dugout, ulcerating crater surrounded by a mere shell of tumor tissue closely adjacent to the rectal and bladder walls. Stone feels that any interference with the nutrition of a tumor is an important factor in the result of radium therapy of tumors. A bulky and necrotic tumor never shows any improvement, and in lesions with an ulcerating crater, radium may cause the premature production of rectal and vesical fistulæ. In a few extremely advanced cases, however, if the nutrition of the tissues appears good, the application of a large amount of heavily screened radium, applied in a pack at some distance from the normal tissues overlying the tumor, will often afford considerable relief from pain. It is in advanced cases, where the parametrial tissues are definitely infiltrated, but where there is a palpable limitation of the tumor process, that radium is effective in arresting the process—relieving pain, stopping hemorrhage and discharge and restoring the general health—the adenocarcinomatous type being more susceptible to the action of radium than the infiltrating epithelioma. The changes produced by an effective dose of radium take place slowly, the tissues becoming edematous and softer by the end of the first week, the discharges sometimes being temporarily increased. By the third week the extra-uterine lesion is less well defined, the pain and discharge gradually diminish, until within two months little, if any, tumor tissue may be felt, leaving finally in many cases only an atrophic uterus fixed in tissue which is indistinguishable from fibrous connective tissue. In some cases a certain amount of tumor tissue may remain, though there is improvement in general health. How long is treatment to be continued in such cases? Under



further application of radium the lesion may improve, but a small ulcerating surface of the cervical mucosa may persist, due to poor nutrition in the surrounding zone of tissue, the age of the patient or overdosage at the first treatment. Radium will convert the borderline lesions, or those in which the growth is largely limited to the uterine wall, into operable lesions, and without surgery it will effect a disappearance of the gross evidences of the disease and restore health in a large number of such lesions more effectively than surgery alone has hitherto been able to do. Early lesions, either of the cervix or body, are rare. However, on the basis of experimental and clinical evidence the application of radium prior to hysterectomy in these early lesions would seem a justifiable mode of procedure. Prophylactic radium therapy after operation is important. It is possible that a number of low-power emanation tubes wrapped in the gauze drainage of the vaginal wound at the time of operation may prove an efficient means.

**Biological and Clinical Evidence of the Therapeutic Value of Radium and Roentgen Rays in Cancer.**—Last year Levin and Joseph reported the results of their investigations on the effect of radium and roentgen rays on cancer cells, by which they showed that radium may deeply impair the proliferating power and consequently the clinical malignancy of cancer cells without producing any change in the morphological appearance of the tumor. The first effect of the rays on a malignant tumor is the inhibition of the proliferating power, in sterilization, as it were, of the cancer cells, the degeneration and destruction of the cancer cells and the formation of the sclerotic connective tissue taking place subsequently under the influence of the rays. In a further recent series of investigations by LEVIN and LEVINE (*Ann. Surg.*, 1918, lxvii, 442) in the Department of Cancer Research at the Montefiore Hospital the above theories were further corroborated. The morphological appearance of radiated tumor tissue is not an absolute criterion of the therapeutic effect produced by the action of the rays on the tumor. While complete destruction of the tumor cells presents the most perfect result of radiotherapy, nevertheless negative morphological findings do not preclude the possibility that the tumor was influenced by the rays. In a series of twenty cases of carcinoma of the rectum which is being prepared for publication *in extenso* by the senior author, the following observation was made: In the cases in which an attempt at a radical operation was made the condition recurred with greater rapidity and malignancy than in those cases in which there was no operation done and only radium and roentgen-ray treatment given or an exploratory operation performed followed by radiations. Similar observations could be made by any surgeon with a large cancer material. Thus pre- and postoperative radiations of cancer as a method of inhibiting the proliferating power and the consequent clinical malignancy of the tumor cells is of undoubted value and presents no danger.

**Treatment of Fibroid Tumors of the Uterus with Radium.**—For the past five years KELLY (*Jour. Med. Soc., New Jersey*, 1918, xv, 145) has been treating fibroid tumors of the uterus with radium, having had altogether 211 cases under treatment, and he has found that all uncomplicated fibroids of whatever size are favorably influenced by

their treatment, which stops hemorrhage, together with menses, the latter either temporarily or permanently, and either causes the tumor to disappear completely or to shrink to very small dimensions. Before beginning radiation he makes sure that the case is one of uncomplicated fibroid tumor, excluding malignancy by curettage and histological examination and appendicitis, cholelithiasis and inflammatory conditions of the tubes and ovaries by careful examination. Of the 211 cases treated with radium at the present time 87 are cured, the tumors having either entirely disappeared or been so reduced as to be insignificant; 14 are so well that, in spite of repeated requests, they have failed to report for examination; in 62 instances the tumors have diminished in size. The last group is not static; it is composed largely of recently treated cases (less than two years), in which the radium has not had time to produce its full effect. The members of this group are constantly augmenting the first group. In addition to these 2 complicated cases are reported unimproved; 8 were operated on after radiation; 2 died of causes unconnected with the treatment; 12 have sent no report; 14 are too early for results and 10 did not complete treatment. Of the 2 cases reported unimproved 1 was complicated by gall-stones and operation advised, but refused; in the other a huge tumor choked the pelvis so completely that abdominal radiation had to be employed. Of the 8 cases operated on after radiation, in 3 cases the fibroid condition was complicated by ovarian cysts, in 2 bleeding was not controlled by a single radiation and, the patients desiring it, an operation was done; in 3 cases there was insufficient reduction of the tumor mass, a calcified uterus being found in one case. The technic as outlined by the author consists in the application of 300 to 500 millicuries of the emanation, covered with a rubber cot, on the end of a uterine sound within the uterus for about three hours. This may be repeated in a few months or an abdominal treatment may be given. For the latter form of treatment one or more grams of filtered radium are used. The package should be placed on the abdomen and shifted about for several hours, giving the skin a minimum and the tumor a maximum radiation. Immediately after treatment there may be nausea for twenty-four hours, some abdominal tenderness and possibly a leucorrheal discharge for several weeks. A second or third treatment is frequently required to bring about amenorrhea. In younger patients a mild treatment is given so that bleeding may be controlled, but menstruation continued. On the basis of his five years' experience the author feels that radium is the treatment of choice in uncomplicated fibroid tumors of the uterus.

**Radium in Gynecology.**—The great value of radium in fibroid tumors of the uterus is further borne out by the experience of WATKINS (*Surg. Clin. of Chicago*, 1918, No. 1, ii, 89). His patient, a woman, aged forty years, suffered from multiple fibroid tumors which made the uterus the size of a three months' pregnancy. Fifty milligrams of radium with 1 mm. brass screening covered by rubber were inserted into the uterine cavity. Three months later the uterus was normal in size, no tumor could be palpated and the patient had skipped the last two periods. In case of chronic metritis, Watkins's results were equally encouraging, the hyperplastic uterus becoming normal in size, two periods following radium insertion, then a cessation for eight months

followed by regular menstruation. In a case of submucous uterine fibroid with cancer, the results were not so good, rectal and vesical symptoms following the application of radium probably because of insufficient screening. During the next three months the deep growth increased rapidly in size, though there was no recurrence of bleeding, discharge or odor, and the superficial wound healed. In a case of extensive inoperable cancer of the body of the uterus there could be no hope of cure, but three administrations of radium were of great palliative benefit, being followed by a marked diminution in pain, a cessation of all offensive discharge and absence of bleeding up to the time of death. He therefore believes that the value of radium as a palliative measure in these very grave cases cannot be overemphasized.

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## PATHOLOGY AND BACTERIOLOGY

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UNDER THE CHARGE OF

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PITTSBURGH, PA.

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**Acute Respiratory Diseases Among Troops, with Special Reference to Empyema.**—BEALS, ZIMMERMAN and MARLOW (*Jour. Infect. Dis.*, 1918, xxiii, 475) report their findings from a study of acute respiratory diseases occurring among troops from September 25, 1917, to June 1, 1918. Out of a total of 9691 admissions to a base hospital, 4443 were cases of acute respiratory infections. The cases occurred in waves with the greatest severity at the crest of each wave. During a period of three months there were 333 cases of measles (including rubella), only 3 cases having complications, otitis media in each instance. Later, when respiratory infections developed, there were not only many cases of pneumonia and empyema, but the cases of measles, though not greatly increased in number, showed severe complications of a respiratory infection, usually streptococcic in origin. Empyema, pneumonia, tonsillitis, otitis media and severe bronchitis were found accompanying measles. The mortality was high, 61.5 per cent., in cases of empyema following measles. When empyema complicated pneumonia the mortality was 38.2 per cent., and in the 22 cases of primary empyema death occurred in 5 cases, or 22.7 per cent. The authors note four distinct types of empyema—fibrinous, serofibrinous, serofibrinopurulent and purulent. The authors found that for a variable period of about a week there was a serofibrinopurulent exudate, and at autopsy there was often found a serofibrinopurulent exudate in one pleural cavity and a fibrinous or serofibrinous in the other. In the majority of cases a streptococcus, usually hemolytic, was the causative agent. The clinical manifestations include rapid and profound toxemia, the rapid formation of, in most cases, a large amount of pleural exudate and a tendency to pocket formation by old and new adhesions in atypical locations. The most marked autopsy findings were the presence of wide-

spread lesions involving serous membranes, severe bronchitis, in the majority of cases, and a type of bronchopneumonia often closely resembling a lobar process. The authors note the importance of an early recognition of empyema, especially in the acute fulminant type of cases. Diagnosis, they state, depends on close attention to clinical progress and proper interpretation of the physical signs. Control of such epidemics depends on sanitation of the barracks, with adequate space and proper separation, especially of those even slightly affected with respiratory diseases.

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**Experimental Chemical Pneumonia.**—Considerable interest surrounds the question of the nature of the pulmonary reaction under different conditions of irritation. WOLLSTEIN and MELTZER (*Jour. Exper. Med.*, 1918, xxviii, 547 and 551) were led to carry on a series of observations upon the reaction developing within the lung when different chemical substances in solution were introduced. Their attention was attracted to these pulmonary lesions during an investigation upon the treatment of lobar pneumonia by local application of chloramine-T to the infected lung. Animals were primarily infected with pneumococcus cultures by bronchial insufflation, and after two hours 5 c.c. per kilo weight of a 1 to 10,000 solution of the antiseptic was run into the bronchi. They found that this solution was injurious to the pulmonary tissue and appeared to intensify the pathological process. When using the antiseptic solution alone they were able to produce a bronchopneumonia, with marked congestion and edema. Leukocytes attended the pulmonary reaction, but very little fibrin was present. At the end of twenty-four hours some resolution was beginning, and it was almost complete on the seventh day. Similar effects were obtained by the use of Dakin's solution. In another series of experiments the use of mercuric chloride in weak solution gave reactions differing somewhat from these, at times being associated with local thromboses. The lesions were hemorrhagic, but they found they were unattended by a true inflammation. Salt solution gave slight or negligible responses, as did also a solution of sodium sulphate. Magnesium salts are somewhat more irritating and caused moderate pulmonary lesions. The authors indicated that the use of magnesium salts is fraught with danger on account of the deep anesthesia and paralysis of respiration.

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**Studies of Bacteriemias in the Agonal Period.**—There are several points of interest in a study of the bacterial flora of the body at the time of death. The occurrence of bacteria in the blood stream during the terminal stages of patients chronically ill serves as an index of the increasing susceptibility, or better, of the loss of the natural resistance against infection. It is often stated, but less often proved, that severe debilitating diseases increase the non-specific susceptibility of the body. In the work of RICHEY and GOEHRING (*Jour. Med. Res.*, 1918, xxxviii, 421) they have studied several phases of this problem. They have demonstrated by taking blood cultures at the time of death that individuals who have been seriously ill over a considerable period of time not uncommonly have a bacteriemia. These blood-stream infections are absent in individuals who have suffered an acute accidental death. The organisms most prone to invade the body are the streptococci and pneumococci. The studies were made on a series of 206 blood cultures

taken not later than ten minutes after death. Positive blood cultures were obtained 76 times, from which 87 organisms were isolated. The pneumococcus was present in 32 cases while the *Streptococcus pyogenes* was present 16 times. Inasmuch as the majority of the cases in which the pneumococcus was isolated were lobar pneumonia, the invasion of the blood stream by the microorganisms took place before the agonal period. They have shown, however, that the bacterial flora of the blood stream may change so that a new infection is introduced upon a previous one during the agonal period. The technic carried out in these studies gave more accurate results than those usually obtained from heart cultures at autopsy.

**Acid Production by Bacteria.**—A number of methods are available to us for the demonstration and determination of the acids produced by the growth of bacteria in carbohydrate media. The majority of methods in use in bacteriology simply indicate the ability of particular organisms to produce acid from a certain carbohydrate. A few other methods which are but rarely used are for the purpose of determining the quantity of acid which is produced after a given time of cultivation. There has always been a certain technical difficulty of determining in a given culture the amount of acid present from day to day and the speed with which the sugar in the medium has been used up. FISCHER (*Jour. Exper. Med.*, 1918, xxviii, 529) has devised an instrument whereby he may graphically record the quantity of acid during the entire period of growth. The author makes use of the acid resulting in bacterial growth to act upon calcium carbonate, and by collecting the gas in a delicately balanced cylinder he obtains a record of the movements of this cylinder upon a revolving drum. The apparatus as devised appears rather cumbersome, although the results are quite striking. In his preliminary study he has tested some of the coli group. By means of the instrument he is able to record the time when acid production begins and the speed with which it then takes place. He is also able to determine the time when the carbohydrate is entirely used up. The onset of acid production varies with the concentration of the sugar and the total quantity of gas liberated by the action of the acid on the calcium carbonate is in direct proportion to the carbohydrate content of the medium. The graphic curves which are recorded by the instrument are interesting, particularly when organisms with a known curve are cultured with other bacteria. Under these circumstances new curves which are at times more difficult of interpretation are obtained.

**Observations on the Presence of Meningococcus in the Blood.**—Within the last years a number of reports have appeared concerning the findings of the meningococcus in the blood stream. These reports dealt with cases of meningitis in which the blood infection was only an incident in the disease. A suggestion, however, was brought forward that the organisms gain entrance to the blood stream prior to their localization upon the meninges. It was the desire of MAXCY (*Jour. Infect. Dis.*, 1918, xxiii, 470) to demonstrate such a preliminary blood-stream infection in cases subsequently developing meningitis as well as in others in whom the blood-stream infection was transient and of an "abortive type," never leading to a meningral infection. For this purpose they studied meningitis "suspects" presenting minor clinical

manifestations. Negative results were obtained in the blood cultures from 27 such cases. However, during the course of the investigations 2 cases of epidemic meningitis were encountered illustrating the relative unimportance of the blood-stream invasion in one and the apparent great importance in the other. In the first instance the meningococcus was isolated within twenty-four hours of the clinical manifestations. In the second case the meningeal manifestations were not apparent until the fifth day of the disease. The meningeal infection yielded to intraspinal serum treatment at the end of three weeks. At this time the meningococcus was isolated from the blood stream and was reisolated on two successive occasions, covering a further period of two and a half weeks. No focus of distribution for the meningococcus could be demonstrated in the nose.

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**Relationship of the Leukocyte Count and Bone-marrow Changes in Acute Lobar Pneumonia.**—In acute lobar pneumonia the clinician pays much attention to the leukocyte count for the purpose of following each case and for indicating the probable outcome. It is well recognized that the number of leukocytes in the circulating blood varies within wide limits during this acute respiratory disease. The low count is often taken as a grave omen in the outcome of the case. On the other hand, fatal cases may occasionally show a very high count. SAMMUELS and LAMBERT (*Jour. Infect. Dis.*, 1918, xxiii, 443) have studied 17 cases of acute lobar pneumonia, with the object of determining the reason for the marked variation in the number of circulating leukocytes. Various authors had previously suggested reasons for the leukopenia, claiming that this state arises from a lack of response on the part of the bone marrow in producing leukocytes. The authors studied the bone marrow of the femur in all of their cases. They were able to compare the leukocyte count during life with the bone-marrow findings. In a few cases a parallelism between the leukocyte count and the character of the bone-marrow was found: that is, when a persistently low number of leukocytes were present in the blood the bone-marrow was aplastic, and when the leukocyte count was high the marrow was markedly hyperplastic. On the other hand, in the majority of cases no such agreement was found. In several cases a striking lack of harmony between the bone-marrow and the blood changes existed. In one case showing marked hyperplasia of the bone-marrow there was a relatively low count, while in another individual, with a leukocyte count from 19,000 to 27,000, the marrow was aplastic. To explain the latter state they indicate that the origin of the leukocytes must have been in the flat bones or in tissues other than bone-marrow. They are at a loss to explain a hyperplasia of the marrow associated with a low leukocyte count. They do not believe that this results from a rapid drainage of cells out of the circulation.

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**Experimental Carcinomata of Animals and Their Relation to True Malignant Tumors.**—Within recent years several investigations on the experimental production of malignant growths in animals have been published, and these reports BULLOCK and ROHDENBURG (*Jour. Cancer Res.*, 1918, iii, 227) subject to a critical analysis, in which especially the claims of Fischer, Fibiger, Stahr and Yamagiwa and Ichikawa are discussed. Bullock and Rohdenburg, experimenting on a large num-

ber of animals, produced by various forms of chronic irritation epithelial growths similar to those described by the above-mentioned authors, in order to ascertain whether these lesions might not be interpreted as hypergenerative processes rather than true carcinomata. The introduction into the stomach of the rat of celluloid balls covered with pins or bristle spines was followed by polypoid and papillary tumors, which simulated the gastric cancers which Fibiger produced by feeding these animals cockroaches. Microscopically these reactions were characterized in general by hypertrophy of the epithelium, with extensive production of keratin and a proliferation and downgrowth of epithelium toward the muscularis mucosa. Not infrequently ulcers and lesions in the glandular portions of the stomach suggesting cystadenomata resulted. When Scharlach R or pine tar was injected into the wall of the stomach or cotton wicks or rubber sponges impregnated with these substances were placed in the viscus, the formation of papillomatous tumors in the glandular portion and lesions resembling epitheliomata in the squamous region occurred in from seven to fifteen days. An attempt to duplicate the papillomatous tumors of the rat's tongue, described by Stahr, which arose after prolonged ingestion of oats, was made by inserting the fine hairs of bearded wheat or foxglove into the dorsum of the tongue. Ulceration about the hairs, with a considerable proliferation and hypertrophy of the lingual epithelium, resulted. Repeated injection of Scharlach R into the region of the papilla vallata gave rise to a metaplasia of the serous and mucous glands of that region, with the production of lesions simulating benign epithelial growths. Lesions indistinguishable morphologically from human epitheliomata were caused by repeated injections of Scharlach R in oil into the skin of the buttocks in rabbits. As a result of their experiments these authors conclude that a typical proliferation and invasive growth in the presence of an irritant form a doubtful criteria upon which to base a judgment of malignancy, and especially when these irritation tumors show no relation to the age of the animal and an absence of continued growth upon removal of the irritation or upon transplantation.

**Importance of the Lymphocyte in Cancer Immunity.**—Much interest has centered about the relation of the lymphocyte to the spontaneous or induced cancer of animals. Da Fanco was among the first to observe that receding tumors in cancer immune animals were constantly surrounded by a zone of lymphocytes, which he assumed had an important bearing on cancer immunity. Others have confirmed these observations. Later it was reported that mice having a resistance to cancer implantation showed a higher number of circulating lymphocytes than in the susceptible ones. These assumptions concerning the relation of lymphocytes to cancer immunity have been put to experimental tests. Inconclusive results have been obtained, inasmuch as various experimenters were unable to agree with the results obtained by others. SITTENFIELD (*Jour. Med. Res.*, 1918, xxxviii, 465) induced a high lymphocyte count in the circulating blood by repeated injections of pilocarpin. These rats were then inoculated with a transplantable rat cancer and the results compared with controls. A passive lymphocytosis was also induced in other animals by stimulating doses of roentgen rays and transferring the collected lymphocytes into a normal animal. These second animals were also inoculated with a rat cancer.

In none of these was the author able to observe any definite immunity in the animals with the hyperlymphocytosis. In another series of experiments the author made use of animals refractile to cancer implantation, reducing their lymphocytes by intensive roentgen-ray treatment. Their immunity to the cancer inoculation was then tested in the hope that a greater susceptibility could be demonstrated. In this he was disappointed. These results are contrary to those reported by Murphy and Morton. The author continued his experiments by a new procedure. In these the author excised the main tumor mass from rats which had been inoculated with tumor. These animals were then given stimulating doses of roentgen rays to increase the lymphocytes and then were reinoculated with their own tumor. He found that these animals did not develop any immunity to their own tumor even though a lymphocytosis was obtained before reinoculation. When the tumor was incompletely excised the tumor grew at the site of the second inoculation and recurred in 48 per cent. at the site of excision. The author concludes that the degree of lymphocytosis had very little to do with immunity to the tumor used in these experiments. In repeating the work of Murphy and Morton the author was unable to confirm the findings relating to the importance of the induced lymphocytosis as a factor in tumor immunity.

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**Spirillosis.**—HARTMAN and LACY (*Jour. Infect. Dis.*, 1918, xxiii, 449) report the bacteriological findings in the case of a young Italian having clinical manifestations suggesting typhoid fever. The patient suffered from a chronic cough and indefinite gastro-intestinal discomfort. There was some diarrhea. His temperature was of an intermittent character and he had general glandular enlargement, with splenomegaly. All tests for a typhoid infection were negative. He had a low red-cell count which continued to be depressed during the period of observation. During life and after death a peculiar organism was isolated from the blood stream. The microörganism was very pleomorphic, developing into long threads and spirals, but often showing short and coccoid forms. The authors were unable to classify the organism.

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## HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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**Physiological Effects of Siliceous Dust on the Miners of the Joplin District.**—LANZA (*Bulletin No. 132, Department of the Interior, Bureau of Mines*) states that there is much pulmonary disease due to rock dust



among the miners of the Joplin district, affecting probably as high as 30 per cent. of sheet ground miners. The amelioration of dust-producing conditions is progressing at a reasonable rate. Living conditions are generally poor, and often needlessly bad. Although miners' consumption and tuberculosis of the lungs are entirely different diseases, as regards the public health, no distinction should be made as to precautions against spread of infection. The prevention of the spread of tuberculous infection, especially to children in the homes of consumptives, is of paramount importance. The combination of hard work with a short dinner period is injurious and unnecessary.

**Report on Attempts to Cultivate the Virus of Epidemic Poliomyelitis.**—WAYSON (*Hygienic Laboratory Bulletin No. 111*, p. 35) cultivated numerous diplococci and streptococci from the spinal cords and brains of human and monkey subjects which showed, clinically and histologically, the findings in acute epidemic poliomyelitis. None of the organisms cultivated reacted in the small laboratory animals nor in the monkeys with clinical or histological evidence of the disease. The attempt to produce Noguchi's and Rosenow's results were negative, although involving approximately 700 primary cultures and 300 animal tests. Wayson states that in view of the not infrequent reports in the literature for many years of myelitis and poliomyelitis experimentally produced by the injection of streptococci isolated from various sources it is remarkable that none were found among his experiments. The negative findings in attempts to reproduce the results of Noguchi and Rosenow, though carrying out their technic as guided by their writings, would suggest that the virus used did not contain organisms similar to those found by these investigators or that the organisms were of unusual sensitivity, and were lost by imperceptibly slight modifications made of the technic. Diplococci and streptococci were found in several samples of ascitic fluid, when cultures were made under a lowered oxygen tension. Therefore the presence of such organisms in cultures, to which has been added raw ascitic fluid, should not be misinterpreted. The organisms are frequently present in small numbers and may require the development of several days' incubation before they become evident.

**Color Blindness: Its Relation to Other Ocular Conditions and the Bearing on Public Health of Tests for Color-sense Acuity.**—COLLINS (*Public Health Bulletin No. 92*) states that color blindness is best detected by testing with colored lights of known spectral composition. It is of great importance to divide the color blind into the dangerously color blind and the harmlessly color blind. This may be done satisfactorily and expeditiously with the Eldridge-Green lantern after gaining an understanding of the principles of the test employed. The Jennings test results in the rejection of a large percentage of subjects who should be accepted, especially among the more intelligent, but it possesses certain lines of examination where great accuracy and classification of color defects are not essential. It should not be used for testing sailors or trainmen. In every-day life among healthy individuals in America, color blindness (excluding the pentachromic) occurs in about 8.6 per cent. of men and 2.2 per cent. of women. Color blindness of a degree dangerous in occupations requiring recognition

of colored signal lights occurs in about 3.1 per cent. of men and in about 0.7 per cent. of women. Among refractive conditions of the eye, color blindness occurs least frequently in eyes apparently without demonstrable refractive error; it occurs most frequently in eyes showing mixed astigmatism.

**Transmission of Poliomyelitis.**—TAYLOR and AMOSS (*Jour. Exper. Med.*, November 1, 1917, p. 745) present evidence toward the solution of the problem of the mode of infection in poliomyelitis by means of secretions from the mouth and nose. This theory was first propounded by WICKMAN (*Beiträge zur Kenntnis der Heine-Medinschen Krankheit*, Berlin, 1907), whose clinical studies disseminated the view of the personal factor in the communication of the virus of poliomyelitis. The occurrence and epidemiological importance of the non-paralytic or abortive cases and of healthy carriers were also emphasized by Wickman. The credit, however, of first calling attention to non-paralytic cases in epidemic poliomyelitis belongs to an American sanitarian, CAVERLY, who recorded 6 cases among a total of 132 cases in the Rutland epidemic of 1894 (*Jour. Am. Med. Assn.*, 1896, xxvi, 1). FLEXNER and LEWIS, in 1910 (*Jour. Am. Med. Assn.*, 1910, liv, 1140), detected the virus in the nasopharyngeal mucous membrane of infected monkeys. KLING, PETERSSON, and WERNSTEDT (*Com. Inst. Med. Etat. à Stockholm*, 1912, iii, 5) injected monkeys with buccal washings from so-called abortive cases and from healthy carriers, with, however, inconclusive results. ROSENAU, SHEPPARD and AMOSS (*Boston Med. and Surg. Jour.*, May 25, 1911, clxiv, 21, pp. 743-748) and others were unable to demonstrate the virus in the nasal and buccal secretions obtained from persons in various stages of convalescence. Recently, AMOSS and TAYLOR (*Jour. Exp. Med.*, 1917, xxv, 507) demonstrated that the nasopharyngeal secretions are able to neutralize an active poliomyelitis virus, which may account for the negative results. In 1913, FLEXNER, CLARK and FRASER (*Jour. Am. Med. Assn.*, 1913, lx, 201) demonstrated experimentally that the parents of E. A., neither of whom showed any symptoms of illness, and who evidently were not suffering from poliomyelitis, nevertheless harbored the virus of the disease in the nasopharynx. E. A. suffered with severe paralytic poliomyelitis, from which he subsequently improved. Hence, the existence of the healthy carrier was established experimentally. The next demonstration was supplied by KLING and PETERSSON (*Deutsch. med. Wchnschr.*, 1914, xl, 320), who studied a family in which one or more healthy carriers of the active virus of poliomyelitis were demonstrated. In these two successful instances, mixed washings were employed for inoculation. TAYLOR and AMOSS studied a family consisting of the father, aged fifty-nine years; mother, aged forty-two years; Carey, aged sixteen years; sister, Hazel, aged thirteen years; two brothers, Everett, aged ten years, and Dwight, aged seven years. The two younger brothers slept in the same bed and in the same room with the elder brother, Carey. They found that only one child—the eldest boy, Carey—was exposed in a locality in which poliomyelitis was epidemic. The exposure took place on June 2. Immediately afterward he returned home, to a village in which no previous case of the disease was known, and mingled freely with his younger brother and sister.

The contacts may be considered to have been intimate in that the three male children slept in the same room, two of them in the same bed. The incubation period in Carey's case was nine or ten days, as he was taken ill on June 12. His brother Everett, six years younger, developed symptoms one day later and passed through what was probably a non-paralytic attack of poliomyelitis. He may be considered as having been infected by Carey some time during the incubation period and to have exhibited a shorter incubation than his brother. The youngest brother, Dwight, was also freely exposed to both older brothers, and exhibited symptoms passing into those indicative of poliomyelitis five or six days later than his brothers. Finally, Hazel, the sister, in age between the two older brothers, and possibly less freely exposed, developed symptoms and muscular weakness last of all, and about ten days after the eldest brother. The incubation periods of the cases therefore probably were ten days or less, and the order of the attacks was such as to indicate successive infection and not a common one. The second feature worthy of emphasis is the detection in this one family of two carriers of the poliomyelitic virus by the inoculation test. One (Everett) was discovered to be a carrier probably following a non-paralytic attack. In the instance of Hazel there is no doubt, first, that she was discovered to be a carrier, and second, that she developed typical poliomyelitis during the period of carriage. Incidentally the nasopharyngeal secretions of Hazel and Everett failed to neutralize the poliomyelitic virus. Taylor and Amoss, furthermore, state that if the view that the mode of infection in epidemic poliomyelitis is by way of the nasopharyngeal mucous membrane and is brought about or greatly facilitated through the operation of healthy carriers of the virus, we may well consider whether in the final analysis every case of the disease does not develop from a carrier. At first this may seem startling, and yet it merely means that after contamination of the nasopharynx with the virus an intervening period exists during which persistence, multiplication, and invasion of the virus take place. In not all contaminated persons does this process become complete; in some the virus may merely persist for a time, in others it may multiply in the nasopharynx (these constitute the healthy carriers of greater or less endurance), while in the exceptional few invasion also occurs. In the latter, symptoms arise, and such individuals compose the class of poliomyelitis cases. In brief, then, a family containing four children, all of whom showed in varying degrees organisms of poliomyelitis, is described. The source of infection and periods of incubation have been followed. Two of the children were proved by inoculation tests to carry the virus of poliomyelitis in the nasopharynx. Of these, one was detected to be a carrier after recovering from a non-paralytic attack of the disease and the other was discovered to be a carrier about five days before the initial symptoms, attended later by paralysis, appeared. The original case from which the three others took origin was fatal; the youngest child, after quite a severe onset, was treated with immune serum, and made a prompt and almost perfect recovery. The nasopharyngeal secretions of 2 of the cases, taken one month after the attack, proved incapable of neutralizing an active poliomyelitis virus. The proposition is presented that every case of poliomyelitis develops from a carrier of the microbic cause, or virus, of poliomyelitis.

**Clinical and Epidemiological Studies on Epidemic Meningitis.**—ROBEY, SAYLOR, MELENEY, RAY and LANDMANN (*Jour. Infect. Dis.*, October, 1918) studied a group of 26 cases of epidemic meningitis which were admitted to the Base Hospital at Camp McClellan, Alabama, between September 27, 1917, and April 4, 1918. They found that the use of a good polyvalent antimeningococcus serum together with four types of monovalent serum for agglutination tests detects more accurately all types of meningococci, in routine work on a large scale, than does either polyvalent or monovalent serum used alone. Most of the meningococcus carriers in a company in which a case of meningitis occurs harbor an organism of the same type as that causing the case of meningitis. It is usually possible to find a chronic meningococcus carrier in a company in which a case of meningitis occurs. Three consecutive negative cultures taken at three-day intervals do not ensure permanent freedom of a carrier from the meningococcus. At least five negative cultures taken at three-day intervals should be required and the carrier cultured at intervals after release. The meningitis at Camp McClellan during the winter is considered to have been a series of sporadic cases, not an epidemic.

**Diagnosis of Epidemic Meningitis and the Control of its Treatment by Rapid Bacteriologic and Serologic Methods.**—COHEN and FLEMING (*Jour. Infect. Dis.*, October, 1918) describe simple, rapid and accurate methods for the isolation and cultivation of the meningococcus as a result of their studies on the subject. They call attention to the fact that the meningococcus is a micro-aërophil. They measured the optimum reduction in oxygen tension for meningococcus cultures. They found that meningococci grow best in an atmosphere composed of approximately 10 per cent. CO<sub>2</sub> and 90 per cent. air. In 500 nasopharyngeal cultures 10.8 per cent. carriers were found by CO<sub>2</sub> and 1.4 per cent. by the usual method.

**Comparison of Methods for the Examination of Water at Filtration Plants.**—NORTON (*Jour. Infect. Dis.*, October, 1918) compiled statistics concerning the methods of water examination in connection with 24 purification plants in this country and found that in no two instances were the methods exactly alike. He states that about two-thirds of the laboratories use gelatin as the medium for obtaining a total count at 20° C. The procedures with this medium are fairly consistent. About seven-eighths of the laboratories use an agar medium for counts at some temperature while 60 per cent. conform to a twenty-four-hour count at 37° C. The composition of the medium is as consistent as possible with ingredients from varying sources. Many differences are found in the methods for the detection of organisms of the type *B. coli*. About 60 per cent. of the laboratories use lactose broth and most of the remainder use lactose bile. In somewhat less than half of the instances the presumptive test only is made while the others use a great variety of confirmatory tests. No definite relation is maintained between gelatin and agar counts. In order to be comparable, data of water examinations must be collected under identical conditions. Since no uniformity in methods exists among the laboratories in this country, bacteriological data of water supplies and water purification processes are not amenable to critical comparisons.

**Further Studies on Bacterium Abortus and Related Bacteria.**—EVANS (*Jour. Infect. Dis.*, October, 1918) reports the results of her studies on methods designed to give the numbers as well as kinds of bacteria of the type of *Bacterium abortus* and related strains found in freshly drawn milk. *Bacterium lipolyticus* and other abortus-like bacteria were isolated from the milk of 10 to 24, or 41.7 per cent. of cows which had not aborted. The cows belonged to a herd in which there was an occasional abortion, but no general outbreak. The same kinds of bacteria were isolated from the milk of 100 per cent. of 12 cows which had aborted as a result of natural infection. *Bacterium lipolyticus* was cultivated from the milk of 66.6 per cent. of these cows and other abortus-like bacteria were cultivated from the milk of 50 per cent. of them. Typical virulent strains of *Bacterium abortus* could not be isolated from the milk of either of the above-mentioned groups. Typical *Bacterium abortus* was found to be present in very large numbers in the milk of 2 cows that had been repeatedly inoculated with a mixture of strains of that organism. It was found only once, in rather small numbers (450 per c.c.) in the milk of another cow which aborted after receiving one inoculation. The data indicate that virulent strains of *Bacterium abortus* are not eliminated continuously in large numbers in the milk of cows which have aborted even though the blood serum continues to react positively to the agglutination test. The author discusses the characteristics of *Bacterium lipolyticus* and other abortus-like bacteria and their relation to the typical *Bacterium abortus*; also the possibility that some of these strains may cause abortions in those cases in which the blood serum reacts negatively to *Bacterium abortus* antigen. The bacterial flora of the udders of a herd in which there existed an outbreak of abortions was found to be abnormal in the large numbers of udders which were infected with streptococci, and it was also abnormal in showing a general infection with a streptothrix. Abortus-like bacteria were found in 66.6 per cent. of the samples of milk. The abortus-like bacteria included 7 acid-producing strains which had never before been found.

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**Streptothrix (Nocardia) Infection of Cows' Udders.**—EVANS (*Jour. Infect. Dis.*, October, 1918) studied the bacterial contamination of cows' milk as it comes from the udder. A streptothrix (nocardia) was isolated from 85.7 per cent. of the infected udders examined. Streptothrices are common saprophytic and parasitic organisms which occur in soil and water and are associated particularly with herbage. They are the cause of many diseases, and infection has in many cases been traced to herbage. Cattle are the most susceptible animals, and the most common diseases caused are lumpy jaw and pneumonia. In human beings the most common infections are about the mouth or in the neck, as the result of oral infection. The next common seat of apparent primary infection was the appendix, and next was pulmonary infection. In the tropics Madura foot is a common disease caused by a streptothrix. Evans states that any comment on the possible sanitary significance of large numbers of a streptothrix in milk would be mere conjecture. Animal inoculation would not give reliable information on this point, for numerous investigators who have studied the streptothrices agree that pathogenicity is not a reliable specific character. The finding

of streptothrices in milk merely adds a fourth organism to the three types of bacteria of a suspicious character already known to occur in milk freshly drawn from normal udders—the streptococci, the staphylococci and the rod-forms of the *Bacterium abortus* type. Thus the streptothrix may prove to be still another source of danger in the use of raw milk as food, and may furnish an additional reason for taking advantage of the safeguard afforded by pasteurization.

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**Prevailing Pandemic of Influenza.**—KEEGAN (*Bulletin No. 44, Division of Sanitation, Bureau of Medicine and Surgery, United States Navy Department*) states that a rapidly spreading pandemic disease was first recognized at the United States Naval Hospital, Chelsea, Mass., August 28, 1918, the first patients coming from the receiving ship at Commonwealth Pier, Boston, Mass. It has been carried to this port from Europe, both by patients and by carriers. It promises to spread rapidly over the entire country, attacking 30 to 40 per cent. of the population and running an acute course of four to six weeks in each community. This disease is characteristic of the ordinary endemic influenza, but is more severe and much more contagious. It is caused by a specific virulent strain of the influenza bacillus, against which individuals of the younger generation have relatively no immunity. In 5 to 10 per cent. of the persons afflicted it develops into a massive and very fatal bronchopneumonia. This pneumonia is primarily caused by the influenza bacillus, this microorganism being recovered from 82.6 per cent. of the lungs at autopsy, in 31.6 per cent. of which it was found in pure culture. The pneumonia is frequently complicated by pneumococcus or streptococcus infection. The disease is characteristic of a sudden and severe toxemia, the influenza bacillus not being in the blood at any stage. The disease is not due to a filterable virus. This was determined by introducing the filtrate of nasal and throat washings from two typical cases into the anterior nares of nine volunteers, with negative results.

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**Rat and Poliomyelitis.**—AMOSS and HASELBAUER (*Jour. Exp. Med.*, October 1, 1918, p. 429) state that their experiments bring out a remarkable similarity between the tests on the rat and those made by Amoss previously on the rabbit. Indeed, it appears that the rat is an even more unfavorable host for the virus of poliomyelitis than is the rabbit, since in the former animal an effective dose of the virus for the monkey was no longer detectable at the expiration of four days. This fact is hardly consistent with the theory that the rat constitutes a natural reservoir in nature of the virus. Rather the experiments would indicate that the rat's organism is wholly unadapted to its multiplication and survival. The central nervous organs and other viscera of six rats, collected in a district in Greater New York in which many cases of epidemic poliomyelitis occurred, have been proved incapable of inciting, on inoculation, experimental poliomyelitis in *Macacus rhesus* monkeys. The virus of poliomyelitis injected into the brain of white rats does not survive there as long as four days in a form or in amounts sufficient to cause infection when inoculated intracerebrally into monkeys. The failure of the virus injected into the brain of rats to incite infection in monkeys is not due to the quantity introduced, since at the expiration

of one and a half hours after the injection the excised inoculation site when injected into the monkey caused typical experimental poliomyelitis. It does not appear probable, therefore, that the rat acts in nature as the reservoir of the virus of poliomyelitis.

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**Further Study of Experimental Parotitis.**—WOLLSTEIN (*Jour. Exper. Med.*, October 1, 1918, p. 377) describes a new series of inoculations into cats of the filtered sterile salivary secretions derived from cases of parotitis. They confirm the observations made by her in 1915-16 and extend them to include the epidemic parotitis occurring in our military forces. Incidentally, confirmatory evidence of the filterable nature of the causative agent of mumps has been obtained. It has been determined that the saliva of man and of inoculated cats, and the inoculated glands of the latter animals, contain the filterable, infective agent. The lesions present in the inoculated organs conform to those previously found. In addition the lymph glands adjacent to the salivary glands on the uninoculated side were sometimes found to be swollen and to exhibit microscopic lesions. Probably the involvement resulted from salivary and lymphatic infections. The "virus" of parotitis was detected most readily in the saliva during the first three days of the disease, less easily on the sixth day and not at all on the ninth day. It was detected also in the blood of patients showing marked constitutional symptoms and in the saliva of a case of recurrent mumps at the periods of enlargement of the parotid glands, but not two weeks after the swelling had subsided. It was not detected in the cerebrospinal fluid.

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**Spirocheta Hebdomadis, the Causative Agent of Seven-day Fever.**—IDO, ITO and WANI (*Jour. Exp. Med.*, October, 1918, p. 435) describe a new species of spirochete, which they call *Spirocheta hebdomadis*, as the specific etiological agent of seven-day fever, a disease prevailing in the autumn in Fukuoka and other parts of Japan. This spirochete is distinguishable from *Spirocheta icterohemorrhagiæ*, to which it presents certain similarities. Young guinea-pigs are susceptible to inoculation with the blood of patients and to pure cultures of the spirochete and those developing infection exhibit definite symptoms suggestive of those of seven-day fever in man. The blood serum of convalescents from seven-day fever contains specific immune bodies acting spirochetolytically and spirocheticidally against the specific spirochetes, but not against *Spirocheta icterohemorrhagiæ*. The field mouse (*Microtus montebelli*) is the normal host of the spirochetes, which have been detected in the kidneys and urine of 3.3 per cent. of the animals examined. The endemic area of prevalence of seven-day fever corresponds with the region in which field mice abound.

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**Report on Antimeningitis Vaccination and Observations on Agglutinins in the Blood of Chronic Meningococcus Carriers.**—GATES (*Jour. Exper. Med.*, October, 1918, p. 449) states that a meningococcus vaccine suspended in salt solution has been given subcutaneously as a prophylactic to about 3700 volunteers in three injections of 2000 million, 4000 million and 4000 to 8000 million cocci at weekly intervals. These doses rarely caused more than the mildest local and general reactions.

Exceptionally a more severe reaction emphasized the presence of an unusual individual susceptibility to the vaccine. In such instances the symptoms were in part those of meningeal irritation and sometimes simulated the onset of meningitis. Specific meningococcus agglutinins have been demonstrated in the blood serum of vaccinated men as compared with normal controls. Moreover, agglutinins have been demonstrated in the blood serum of chronic carriers of the meningococcus. Evidence is thus brought forward that the relative immunity of chronic carriers to epidemic meningitis may be due to the presence of specific antibodies in the blood stream.

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**Action of the Extreme Ultraviolet of Tropical Sunlight on the Complementing Power of Serum.**—BOVIE (*Jour. Med.*, July, 1918) states that the protection which the photosensitive components of the protoplasm enjoy because of the red color of the blood is undoubtedly of very great biological importance. Notwithstanding the obviously painful nature of this relation, teleologism may be avoided by saying that the blood, since it is red, *i. e.*, highly absorbing at the more refrangible end of the spectrum, does protect our bodies from the actinic solar rays (at least in the absence of optical sensitization) quite as efficiently as we protect our photographic plates by using a ruby light. Whether any more useful purpose is served by the red color of our blood is yet to be determined. If the red cells are to be an efficient protection against the actinic rays of the sun it is essential that they be composed of substances possessing considerable photostability. Experiments reported by Dr. A. W. Sellards show this to be the case. The protection which may be offered by the pigments of the skin have not been discussed in this paper, because the experiments have not been carried on in such a manner as to obtain data concerning this phase of the subject.

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**Protective Therapy for Varicella and a Consideration of its Pathogenesis.**—HESS and UNGER (*Am. Jour. Dis. of Children*, July, 1918, xvi, 34-38) found it possible to bring about immunity to varicella by means of an intravenous injection of the contents of the vesicles. In thirty-eight instances in which this was carried out it failed to protect in only one case. The authors state that vaccinations of this kind induce neither local nor systemic reaction. The acquisition of immunity likewise indicates that the specific virus is contained in the vesicles. A simpler method of therapy, the application of the lymph to the broken skin or mucous membranes, failed to bring about satisfactory immunity, although it also occasioned no disorder. These investigations have a secondary bearing as to the natural portal of entry of the varicella virus into the body. As the skin and the mucous membranes can be excluded in this connection it would seem most probable that the virus enters by way of the respiratory tract and that contagion comes about through the air. This mode of infection would account for the almost unexampled communicability of this disease.

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**Scurvy.**—(*United States Naval Medical Bulletin*, July, 1918). Extensive outbreaks of scurvy have occurred on land during wars since the Middle Ages; thus 55 out of 143 epidemics analyzed by Hirsch were during hostilities. Three previous endemics in prisoners' camps have



been recorded: (1) 159 cases among 10,000 French prisoners in the Ingoldstadt camp in 1871, (2) among prisoners at Port Blair in the Andaman Islands and (3) among the Hereros in the Southwest African War, the last two being the more serious. In recent wars hygienic measures have prevented scurvy, and only in Russia or countries in which the disease is endemic or sanitary methods are in grave default are large endemics probable. The outbreak among the Austro-German prisoners in Turkestan was much more extensive than in former wars; Disqué saw 504 cases in one military hospital and in a camp of 4000 prisoners there were 754 cases, or 19 per cent. The largest number of cases occurred in March (222) and April (158), when night blindness also increased. The incidence of this large number of cases in the spring was attributed to bad hygienic conditions and the absence of green vegetables in the winter. Giugni observed an outbreak of what appears to have been scurvy among the Italian troops, especially the infantry, at a high elevation in the Dolomite Alps, beginning in June, 1916, increasing during July, reaching its acme in August, declining in October and November and disappearing in the winter. The disease spread in an epidemic fashion to neighboring areas, but not to the same extent as in the original focus, and some sporadic cases were seen at the base. The duration of symptoms ranged from two weeks to two or three months; there were no fatal cases. During a mild epidemic of scurvy among soldiers, Tuchler found that at least 60 per cent. of the patients, including those already ill for three or four weeks, were in an excellent state of nutrition. So far from there being any relation between the severity of the attack and the general state of nutrition, many soldiers in good condition showed the most extensive hemorrhages in the skin and gums. The occurrence of an initial rigor, the continued fever, and the microscopic data led Tuchler to support the view that scurvy is an infective disease, but he does not agree with Much and Baumbach that the infection is conveyed by lice, as all his cases appeared after satisfactory measures for combating this pest had been established. The influence of dark and damp quarters in producing the disease was shown by the cessation of fresh cases when stationary warfare was succeeded by active campaigning in the field and by Weinberger's experience that a regiment provided with a good diet was regularly attacked by scurvy when sent into dark quarters.

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**Psychiatric Material in the Naval Prison at Portsmouth, N. H.—**  
JACOBY (*United States Naval Medical Bulletin*, July, 1918, No. 3, xii) found among 150 admissions of general court-martial prisoners to the Naval Prison that 66.6 per cent. of the cases fell in psychopathic groups. Attention is called to the fact that 99 of the 150 individuals were in the navy less than one year before they arrived at the prison. In order of frequency the following diagnoses appear: subnormal, 22.6 per cent.; hysteria, 12 per cent.; constitutional inferiority, 6 per cent.; psychopathic personality, 5.3 per cent.; chronic alcoholism, 4 per cent.; dementia precox and cerebrospinal syphilis, each 2 per cent.; manic depressive insanity, anxiety neurosis and epilepsy, each 1.3 per cent. In the 50 cases classed as having no psychiatric condition the cause for commitment to prison was given as "alcohol" in 20 per cent.; a "bad gang" in 14 per cent.; and "women" in 10 per cent. The offences

represented ranged from absence over leave to murder and 56 per cent. of the total offences were of a military nature and not such as would bring the offender into a civil court. He concludes that attention should be directed to the character of the offender as well as to the offence before a man is sent to prison; that the prison population of the navy might be reduced one-half by careful psychiatric examination of each man at the beginning of his naval career and a further reduction of 12.6 per cent. is possible by thorough examination of all offenders before being brought to trial, with the disposition of psychopathic cases through medical channels.

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**Etiology of Epidemic Poliomyelitis.**—TSEN (*Jour. Exper. Med.*, September, 1918) has isolated streptococci from the central nervous system of monkeys dead of poliomyelitis and also from the central nervous system of monkeys dead of other causes, as well as from the brains of normal rabbits. He states that streptococci isolated from poliomyelitic monkeys do not differ from those isolated from monkeys and rabbits dead from other causes. An etiological relation has not been established between streptococci and poliomyelitis. At several times an organism has been isolated that was similar to the globoid bodies culturally, morphologically, and in straining reaction, but the author has not been able to carry it along for more than three generations. The pathogenicity of these organisms has therefore not been tested on monkeys. He has not been able to produce typical lesions of poliomyelitis in rabbits by the injection of either the poliomyelitic virus or streptococci.

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**Experimental Test of Nuzum's Antipoliomyelitic Serum.**—AMOS and EBERSON (*Jour. Exp. Med.*, September, 1918) state that the antistreptococcic serum of Nuzum and Willy has failed to show in the monkey neutralizing or therapeutic power when applied by their methods against small doses of the virus of poliomyelitis. Under the same conditions the serum of monkeys recovered from experimental poliomyelitis proved neutralizing and protective. The experimental and other evidence adduced by those who regard the streptococcus as playing an essential part in the pathology of epidemic poliomyelitis and the antistreptococcic sera as exhibiting therapeutic properties for man and monkeys is regarded as imperfect and inconclusive.

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ORIGINAL ARTICLES

CLINICAL STUDIES IN CUTANEOUS ASPECTS OF  
TUBERCULOSIS.

II. THE DIAGNOSTIC AND CLINICAL RELATIONS OF CERTAIN  
TUBERCULIDS.

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THE tuberculid is a cutaneous lesion of exceptional interest to the pathologist, the internist and the general diagnostician. The term was devised by Darier to describe a group of lesions associated with tuberculosis of the viscera, which, while accompaniments of this disease clinically, did not exhibit necessarily the characteristic pathological anatomy of tuberculosis in other structures. Thus, for example, lupus vulgaris is a true tuberculosis of the skin, with the histological architecture associated with the disease in other parts of the body. The papulonecrotic tuberculid, on the other hand, is a localized non-specific type of inflammatory reaction, the individual lesions being papules occurring by preference upon the extremities, each distinguished by a central necrotic plug, which, on separation, permits the healing of the lesion with the formation of a punctate, atrophic scar. Upon the etiology of tuberculids a large amount of clinical and experimental work has been done. The relative degrees of association of the various types with tuberculosis have been widely studied. Lichen scrofulosorum, a grouped, follicular, papular eruption, has been clinically and experimentally demonstrated to be a tuberculid. The papulonecrotic tuberculid, another type of cutaneous lesion, is now generally accepted as of

tuberculous origin, so that its use as a diagnostic criterion in the identification of tuberculous lesions, frank or occult, is justified by a large body of clinical and experimental evidence. Two types of papulo-necrotic lesions with distinguishing characteristics are given separate names in the majority of dermatologic texts. These are acnitis, the papulonecrotic tuberculid of the face, first clinically defined by Barthelemy, and folliclis, the papulonecrotic tuberculid of the extremities. Of the two, the former is stated by Jadassohn to have the more distinctively tuberculoid histopathological structure. A third type of tuberculid, one degree removed, so to speak, from final demonstration as a manifestation of tuberculosis in the skin, is the so-called erythema induratum of Bazin, a plague-like lesion prone to ulceration, most often found upon the lower extremities, especially the calf of the leg. The tuberculous character of this lesion, in spite of its inflammatory architecture, is now practically conceded, especially as a result of the recent rapid advances in methods of demonstrating the tubercle bacillus by animal inoculation, antiformin digestion, etc. It also is a lesion of marked diagnostic value in the recognition of obscure tuberculosis. A number of other lesions for various reasons are now held to be tuberculids, among which might be mentioned acne scrofulosorum, pityriasis rubra pilaris, certain exfoliative erythrodermias, acne necrotica, acne cachecticorum, lupus pernio and the sarcoids. The possible tuberculous relations of lupus erythematosus and of purpura, erythema multiforme and erythema nodosum are also subjects of recent and active discussion. The material of the Mayo Clinic seems to be exceptionally rich in tuberculids, and this has afforded a number of opportunities to study the clinical and diagnostic relations of those types now accepted as on a definitely tuberculous status—the papulonecrotic tuberculid and erythema induratum. I have, moreover, discussed 8 of the cases in the present series of 30 from the standpoint of the relation of erythema nodosum to tuberculosis.\*

The crux of the discussion of tuberculids among dermatologists and immunologists has centered about their pathogenesis. This point was admirably brought out in Jadassohn's masterly review of the subject just before the War. It was also dealt with in a symposium before the meeting of the Dermatological Section of the American Medical Association (1918), the discussions to appear in the *Journal of Cutaneous Diseases* during the year. The problem of investigators has been to explain how a lesion, which in pathological architecture is not tuberculous, can present such an unvarying association with a tuberculous focus as that found in the papulonecrotic and erythema induratum types of tuberculids. The theories on which work was at first conducted followed the familiar toxic lines and ascribed the cutaneous lesions to tuberculo-

\* Study I, "Tuberculous" purpura, erythema multiforme and erythema nodosum.

toxins elaborated at a distant focus. The development of experimental methods has, as already intimated, relegated this theory increasingly to the background and brought forward more and more convincing evidence that the tubercle bacillus itself, probably hematogenously distributed, is responsible for the individual lesions of a tuberculid. While organisms are exceedingly difficult to demonstrate in these tissues, positive results are claimed, and the percentage of successful animal inoculations is rising above the margin of experimental error for this mode of establishing tuberculosis. But the demonstration that the tubercle bacillus, whether in viru-



FIG. 1 (191446).—Acnitis, the papulonecrotic tuberculid of the face. Patient had had tuberculous peritonitis. Note the central necrotic plugs and the uniformity in size and age of the lesions. The crop appeared following quinsy, was treated as *acne vulgaris* and was ascribed by the patient to *nux vomica*.

lent or attenuated form, is responsible for the lesion is not adequate to explain why in one case hematogenously distributed bacilli gave rise to tubercles and epithelioid changes and in others to merely non-specific inflammatory reactions with necrosis or to fibroid changes of a quasi-neoplastic instead of granulomatous character. In animal experimental work it has been shown that the tubercle bacillus can persist as an embolic invader in veins without setting up more than trivial changes (Liebermeister). Through the work of Saeves in trichophytoses a similar condition of insusceptibility of tissues has been recognized in these diseases. One explanation, that of a difference in the virulence of the invading organism, has had

numerous proponents. It has, however, gradually given place to an explanation based on the different reactivity of different persons and even of different tissues to the organism. In other words, cutaneous allergy or hypersensitiveness has been invoked to explain why one person develops lupus vulgaris, another a papulonecrotic tuberculid, another lichen scrofulosorum and still another, perhaps, a sarcoid. The importance of the allergic factor was effectively demonstrated in the experimental work of Rist and Rolland, and there can be little doubt that while its significance may be overestimated by some investigators, it is one of the best available explanations of the phenomena. For a fuller consideration of the experimental work underlying this theory, reference should be had to the studies of Gougerot, Rist and Rolland and Zieler.

Thus far the principal emphasis has been placed on tuberculin and tuberculo-toxins themselves as the agents that sensitize the tissues to the hematogenously distributed bacilli. Ingenious explanations have been devised to account for the observed failure of certain persons with tuberculids to react to tuberculin in the von Pirquet or intradermal tests. These follow the immunological conceptions applied in explaining the failure of extreme stages of tuberculosis to react to tuberculin. Thus far, however, little account has been taken of the possibility that sensitizing agents other than tuberculin may be responsible for a part of the allergy which makes a tuberculid possible, and that the person who does not react to tuberculin fails to do so because he does not owe his sensitiveness to tuberculin but to some other toxic substance or bacterial product. This point will be raised again in pointing out the association of tuberculids with pyogenic foci of infection, as evidenced in this series. The mechanism of the allergic reaction which results in the formation of the papulonecrotic tuberculid is, roughly, as follows:

Bacilli are carried by the blood stream to a hypersensitive skin and deposited at points where the circulation best favors the lodgment of an embolus—namely, in the extremities. At once a local anaphylactic reaction is set up, an inflammatory papule forms and at the point where the reaction is most intense disintegration of the tissues occurs with central necrosis. In the reaction the organisms which precipitated it are largely destroyed, which accounts for the excessive rarity of their demonstration. The pathological picture is that of an acute inflammation and is practically identical in the papule of a von Pirquet reaction, the papule of folliclitis or acnitis and the lesions of erythema induratum. While a tuberculid may not be tuberculosis cutis histopathologically, it is due to the tubercle bacillus, and as such is evidence of its presence in the body. This, in effect, summarizes the trend of modern opinion. It should not be forgotten that, like all generalizations, this one has its borderline, and that it is possible to demonstrate lesions which clinically are tuberculids yet have the architecture of tuberculosis (Harris's case

of dermatitis nodularis necrotica as illustrated in Pusey's *Principles and Practice of Dermatology*).

Tuberculids of the papulonecrotic and erythema induratum type, when recognized, have a considerable value to general diagnosticians as earmarks of obscure tuberculosis. An understanding of their pathological and clinical background often throws much light on elements in the patient's general condition, which may be ignored or misinterpreted. A preliminary description of the type here considered will be of assistance in a comprehension of these relations.



FIG. 2 (200229).—Acnitis, the papulonecrotic tuberculid of the face in a patient with tuberculous adenitis, showing the involvement of the ear by the tuberculid. The black spot in the helix is an active lesion. "Moth-eaten ear."

It must be borne constantly in mind that the distinction between types of papulonecrotic tuberculids—that is, folliclis—the papulonecrotic tuberculid of the hands, or acnitis, that of the face, is largely for clinical convenience, and that one is not exclusive of the other. All the various forms may be present at the same time in the same person or in succession at different periods of his history. The identification of the elementary lesion of a tuberculid, or in fact of any dermatosis, is the first requisite to a diagnosis. The elementary papulonecrotic lesion is exactly what its name indicates. Whether occurring on the face, the hands, the buttock, the legs, the toes, the ears, it is an inflammatory papule exhibiting, in fully developed form, a central necrotic plug of tissue, usually dark in color. In its earlier stages the papule may vesiculate, later drying enough to show the necrotic plug. The plug may, in the later stages

of the lesion, either suppurate out or be picked out by the patient, leaving a conical depression which heals, producing a punctate atrophic scar. The inflammatory process which produced the papule also gives rise to a ring or collarette of hyperpigmentation about the scar, which persists for periods of months or even years in certain situations, especially on the lower extremities, where stasis accentuates the process. A papulonecrotic lesion may vary in size from a large pinhead in folliclis to a pseudofuruncular lesion several centimeters across in dermatitis nodularis necrotica, but if careful examination is made the primitive or essential lesions can usually be found.



FIG. 3 (226884).—Various types of folliclis, the papulonecrotic tuberculid of the hands. An active lesion on the fourth finger of the left hand. Note the typical crater left on removal of the necrotic plug. Patient with tuberculous adenitis.

Failure to recognize papulonecrotic lesions or their scars is quite as often due to faulty methods of examination as to unfamiliarity with the lesion. The localizations and sites of predilection of the lesions are often not inspected by the internist, who is interested in percussing the chest or palpating the abdomen. Instead of making a purely objective examination of the entire body, the busy diagnostician, guided by the history, is likely to overlook the moth-eaten ear of acnitis unless he is expecting gouty tophi. In the same way the backs of the terminal phalanges and the tips of the fingers, the favorite localization for the form of papulonecrotic tuberculid known as folliclis, are seldom the subjects of painstaking inspection by general diagnosticians. Punctate atrophic scars about the



elbows and the extensor surfaces of the forearms are attributed to furuncles and trauma instead of to the tuberculid responsible for them. A poor light, as well as cursory inspection, is responsible for many misconceptions of these lesions. Surprising and entirely unwarrantable operative interference may be practiced upon tuberculids of the leg through insufficient observation or faulty interpretation. Incisions for drainage, excisions with suture, skin grafts and transplants, excisions for diagnosis, with a report of "fibroma," "inflammatory tissue," etc., are frequent. The exquisite tenderness of many of the larger leg lesions combined with central softening is misinterpreted as osteomyelitis or furunculosis and subjected to operative trauma.

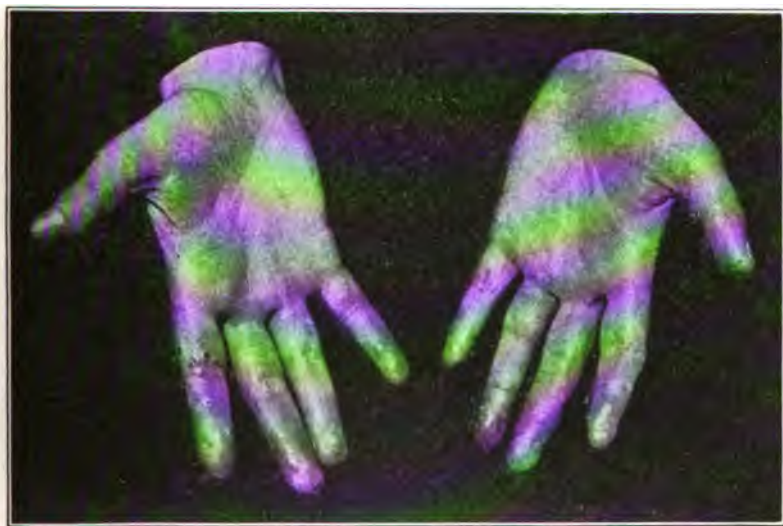


FIG. 4 (212370).—Folliclis in a patient with erythema induratum. Note the various stages—a fresh papule on the patient's right little finger, vesicle formation and beginning necrosis on the left little finger, active lesions with central necrosis on the right index and middle finger, scars on the left index and middle fingers.

Erythema induratum is in a sense only an exaggeration of the papulonecrotic lesion. In fact, the larger lesions often seem to be produced by a confluence of smaller nodes. The typical lesion is an erythematous to violaceous plaque usually several centimeters in diameter, firm, indurated and somewhat tender. By predilection these lesions are said to appear on the posterior aspect of the leg in the region of the calf and ankle, but this localization in my experience is by no means constant. Lesions varying all the way from the small necrotic centered papule, through the breaking down nodule to the typical ulcerating plaque may be found scattered about the lower, and at times even the upper, extremities. In fact, the presence

of papulonecrotic lesions is a material aid in diagnosis of a solitary ulcerative plaque of erythema induratum.

The scars of tuberculids are in many ways quite distinctive. This is especially true if their distribution is limited to one or the other of the sites of predilection. A number of these sites with their characteristic lesions and scars are illustrated in Figs. 1-8, 11, 12, 14, 15, 18 and 20. The scar is never contractile or distorting, and in the peculiar punctate atrophy produced may suggest that of a variola, though it is usually deeper.

#### SUMMARY OF DIFFERENTIAL DIAGNOSIS.

*Papulonecrotic Tuberculid of the Face—Acnitis.* This condition is to be distinguished from acne vulgaris by the circumscribed papule with central necrosis as distinguished from a pustule or infected comedo and by the uniformity of the lesions, which tend to appear in crops and hence to be, to a considerable extent, of the same age and size. The moth-eaten ear, due to papulonecrotic lesions in this site, is illustrated in Fig. 2. The absence of comedones and seborrhea and of transition lesions from comedone to pustule is significant. Acute acnitis may strongly suggest variola from which its course distinguishes it.

*Papulonecrotic Tuberculid of the Extremities—Folliclis.* When limited to the hands and feet, there is practically no other lesion which closely simulates it. In the vesicular stage the marked inflammatory papule which forms the bulk of the individual lesion, and the tendency to become hemorrhagic distinguishes it from the sago-grain vesicle of dysidrosis, pompholyx or "sweat eczema," which moreover does not leave scars. In the case of folliclis the patient describes a highly characteristic sign—a feeling as if a thorn were pressing into the flesh when the papule is pressed upon. Their small size and uniform appearance and a frequent tendency to localize in faceted patches or on the dorsal surface of the phalanges, help to distinguish the scars from those of trauma. In cases with marked vasomotor disturbance the diagnosis of Raynaud's disease may be made through failure to observe the scars or to get a careful history of the course of the lesion. Frost-bite is a more diffuse erythematous lesion. Lupus pernio may temporarily simulate folliclis, but the distinction can be made by a search for the elementary lesion and its evolutionary steps as outlined above. The papulonecrotic tuberculid of the trunk is frequently mistaken for furunculosis and for severe acne vulgaris. Here again the search for the elementary lesion reveals it not as a comedone on a seborrheic base but as a papule in which vesicle formation may occur but is usually abortive and in which pustulation is usually secondary to the formation of the dry, hard, necrotic central plug. The large nodules undergo actual ulceration and heal slowly, suggesting ecthyma and

in the pustular phase, a pustular lues. (The absence of transition stages from comedone to pustule eliminates acne.) On the arms and trunk scratch papules must be distinguished. The scratch papule is a secondary infection of a previously produced excoriation, and uninfected or recent excoriations, dried bloodstreaks, linear abrasions and scars can usually be found. Parasites produce the picture of a scratch dermatitis. The nodular lesions of prurigo and lichen urticatus can be distinguished by the fact that they have no central necroses though they show scratch excoriation. They are



FIG. 5 (228772).—Folliculitis localising at points of greatest trauma. Patient with tuberculous glands.

also accompanied by other evidences of dermatitis, or by wheals and multiform erythematous lesions. The pruritic nodules of Hodgkin's disease may suggest a tuberculid, but their intensely pruritic character and the multiple evidences of scratching, including the history of violent itching, together with the absence of central necroses, eliminate the tuberculid. The nodules of Hodgkin's disease do not primarily localize on the extremities. I have known a generalized tuberculid to be diagnosed a psoriasis in the presence of marked crusting, the diagnostician forgetting that psoriasis does not produce scars.

*Papulonecrotic Tuberculids of General Distribution.* These lesions may occur in showers, especially involving the trunk. Their tendency to show a vesicular stage and the necrosis as distinguished from pustulation helps to eliminate a pustular syphilide. The diagnosis of this type of lesion may offer great difficulties, and not infrequently the conclusion must depend upon collateral evidence of the presence of tuberculosis and the absence of syphilis and upon recurrence and chronicity. One such case in my series yielded a positive Wassermann reaction on several occasions, and only the recurrence of the lesions through a period of years and the final

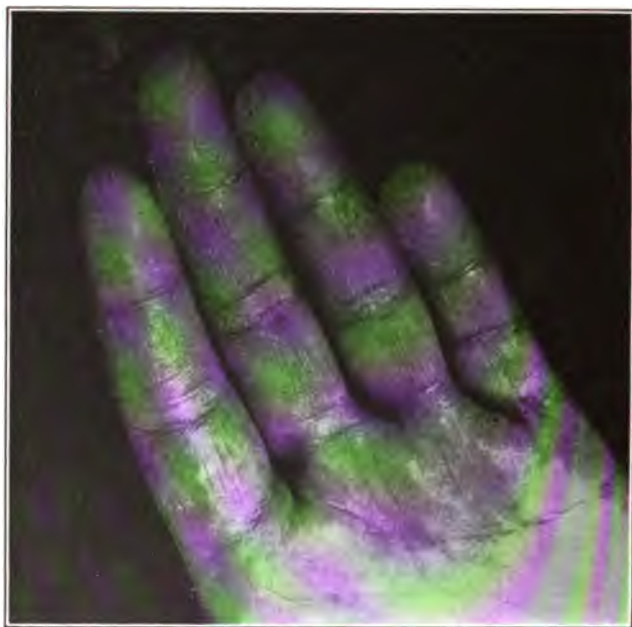


FIG. 6 (230740).—Facetted, grouped scars of folliculitis, index, middle (tip) and fourth fingers. Vasomotor abnormalities, tuberculous adenitis.

occurrence of typical necrotic papules made the differentiation possible. The scars of a widely distributed tuberculid may suggest those of a pustular syphilid so strongly that serious mistakes may be made. In one such case a positive Wassermann and a mass of glands which cleared under arsphenamin seemed to establish a diagnosis which was reversed by later findings.

There is a distinct tendency for papulonecrotic tuberculids to occur at points of trauma. This fact has, in my experience, led to confusion with epidermolysis bullosa hereditaria, especially when lesions were localized on the elbows. One distinctive site of lesions in epidermolysis bullosa hereditaria, over the thyroid cartilage of

the larynx from collar trauma, I have never known to be the site of tuberculids not involving the face. Moreover, the bullous phase of epidermolysis is much more marked than the vesicular phase of tuberculids, which is often abortive. Nevertheless, the scarring produced by the two conditions may have many points of similarity (Fig. 6).

*Erythema Induratum.* This condition seldom occurs alone. It usually is associated with papulonecrotic lesions that may group to form larger plaques. The differentiation from nodular lues depends first upon the tendency of the lesions to symmetrical dis-



FIG. 7 (186129).—Scars of folliclis, dorsal surface of fingers. Two involuting lesions on index and middle fingers. Positive Wassermann but no clinical evidence of syphilis.

tribution on both extremities, and second, upon the multiplicity of the lesions and their lack of configuration, that is, their irregular shape and arrangement as distinguished from the grouping into typical arciform or polycyclic arrangements observed in lues. The scars exhibit the same peculiarities (Fig. 7). From gumma of the pretibial region, the solitary character of the gumma and the preference of erythema induratum for the posterior surface distinguish it. It should be remembered, however, that gummas may also be symmetrical and multiple. Multiple infarctions in the skin or anemic ulcers are usually only associated with high degrees of thrombotic occlusion of the vein, which can be seen and palpated

and with suggilation and hemorrhage into the skin and even multiple areas of gangrene. Erythema nodosum is usually distinguished from erythema induratum by the tendency of the latter to ulcerate, and to occur by preference on the posterior surface. As a matter of fact, all stages in the transition from erythema nodosum to erythema induratum both as regards morphology and localization, may be seen in subjects with a tuberculous background, so that some of the distinctions are artificial. Streptococcal or diphtheroid erythema nodosum of the Rosenow type, however, does not ulcerate and the process is, in general, more acute, the nodes more brawny and edematous, and the hemorrhagic and ecchymotic changes and edema more marked than in the tuberculous type. A resumé of this aspect of the problem may be found in the discussion of tuberculous erythema nodosum in the first study of this series.



FIG. 8 (171947).—Papulonecrotic lesions on the foot and ankle of a patient who also had erythema induratum. Note the nodules that have not yet undergone central necrosis, as well as the necrotic lesions with black central plugs.

Ulcerative erythema induratum is to be differentiated from noduloulcerative syphilids again by its tendency to symmetry, which, however, is no more invariable than is asymmetry in lues. The luetic ulcer has a configuration which can be recognized by practice as segmental or arciform. The erythema induratum ulcer is irregular and nondescript. Instead of a sharp margin closely bordered by normal skin, the erythema induratum ulcer is usually undermined, has a thin grumous or hemorrhagic discharge, and is surrounded by bluish scrofulodermatous sodden tissue. There is

usually no definite gummatous slough as in lues. The concomitant occurrence of papulonecrotic lesions and nodules greatly assists in the recognition of erythema induratum. The typical chronic varicose ulcer is easily differentiated by its rigid scar tissue border, its flat open floor of anemic granulations and the usual regularity of its margin. Epithelioma is usually unilateral and has a highly characteristic nodular and rolled pearly margin.

A word of warning should be given as to the use of arsphenamin in an attempt to make a differentiation between a tuberculid and a syphilitic lesion by therapeutic test. Tuberculids, as will be seen in a subsequent paper, respond rapidly to this form of medication, so that a false therapeutic effect is produced which may subject the patient to prolonged treatment for a non-existent lues.

#### CLINICAL RESUMÉ OF THIRTY CASES OF PAPULONECROTIC TUBERCULID AND ERYTHEMA INDURATUM.

The series of cases collected by the writer during the past two years illustrates in a convincing way the association of these conditions with tuberculosis. Of the thirty cases 80 per cent. were women. This preponderance of women over men has been recognized by others. In a series of 100 cases of tuberculous adenitis reviewed in connection with this study a similar proportion of 64 per cent. women and 36 per cent. men was observed. The youngest patient was ten years of age, the oldest fifty-one. Of 13 cases in which data were available the onset of the tuberculid had been in the second or third decade of life in 12, corresponding in this particular to the period of greatest incidence of signs of systemic tuberculosis.

Eighty-three per cent. of the 30 patients bore evidence of past or present lesions of the papulonecrotic type. Three had lesions on the face (acnitis), 12 had lesions or scars on the hands (folliclis), 15 had papulonecrotic lesions on the legs and 9 had them on the trunk. Only 2 patients presented an erythema induratum uncomplicated by another tuberculid. One of these had apparently a tuberculosis verrucosa cutis and the other had undoubted tuberculous adenitis. It is apparent that in its association with other more definitely proved tuberculids in this series, erythema induratum establishes, still further, its claim to a tuberculous origin.

#### RELATION OF THE CUTANEOUS LESIONS TO SYSTEMIC TUBERCULOSIS.

*History of Tuberculosis in the Family or Patient.* A definite history of tuberculosis in the family, sufficiently direct to bring the patient into contact with it, was given by one-fourth of the cases (23 per cent.). Somewhat more than one-third of the patients had been diagnosed as tuberculous previous to their examination in the

clinic. The diagnosis was usually based upon adenopathy rather than on pulmonary or other signs.

*The Objective Manifestations of Tuberculosis.* It is to be understood that tuberculids as signs of tuberculosis are excluded. Fifty-seven per cent., or more than half of the entire series, showed incontrovertible systemic objective signs of tuberculosis, usually in such numbers that had any one sign been insufficient the others would have confirmed the diagnosis.

Thirteen per cent. of the cases were rated as disputable, and 30 per cent. presented no definite signs. Table I, summarizing the disputable and occult cases, is here appended.

TABLE I.

## DOUBTFUL CASES.

- Case A202732—Erythema nodosum; loss of weight; doubtful lung lesion as revealed by x-ray and physical examination.
- Case A212370—Tenosynovitis, tuberculous(?) (folliclis, erythema induratum).
- Case A188556—Erythema nodosum and erythema multiforme. Enlarged right cervical glands; temperature and lung signs.
- Case A224920—Family riddled by tuberculosis; patient underweight; asthenic; well-defined signs in right apex (folliclis, fingers and toes).

## OCCULT CASES.

- Case A39183—Obscure anemia; inflammatory changes in abdomen; positive and negative Wassermann at various times, menorrhagia; headaches; generalized papulonecrotic tuberculid.
- Case A197825—Florid, obese girl; no signs of tuberculosis; erythema induratum.
- Case A221958—Positive Wassermann without history or evidence of syphilis; lupus erythematosus of the face; folliclis, scars on fingers.
- Case A218528—Anemia, persistent; marked loss of weight; erythema induratum and papulonecrotic tuberculid of the legs.
- Case A201284—Anemia, pernicious (?); extreme hyperpigmentation; cachexia; tuberculid of the legs; lupus erythematosus; adrenal tuberculosis(?).
- Case A171947—General examination negative; obese, well nourished woman; extensive papulonecrotic tuberculid of the legs with erythema induratum.



- Case A63167—Iritis in childhood; tuberculosis of the knee (?); three weak positive Wassermanns, without evidence of lues; alveolar abscess, otherwise negative; papulonecrotic tuberculid of legs and elbows; erythema induratum.
- Case A186129—Repeated positive Wassermann; exposure, but no evidence of lues; folliclis of hands; scars of papulonecrotic tuberculid of the body.
- Case A233765—Obese girl, no signs of tuberculosis, but von Pirquet strongly positive; erythema nodosum and induratum; legs and arms involved, with purpuric lesions.

The occult cases form a group of special interest. The mere fact that a gross focus of tuberculosis cannot be demonstrated is of course not an evidence that such a focus may not exist, in the retroperitoneal glands, for example, or in the uterine adnexa.<sup>6</sup>

Two of our patients gave histories suggestive of such a focus but in the absence of operative exploration the focus could not be demonstrated. Four of the 9 occult cases were in florid, rather obese persons, of a type recognized as predisposed to some extent to tuberculous infection.

One-third of 27 cases in which radiograms of the thorax were made showed evidence of pulmonary tuberculosis. The involvements were largely apical, with calcification and signs of healing in several. The importance of a tuberculid as a diagnostic lead for the internist can be appreciated from such a finding. Four cases showed doubtful x-ray signs of little independent value. One-third of the cases likewise presented physical signs suggestive of pulmonary tuberculosis. Both physical and x-ray findings were present in 5 (17 per cent.) of 29 cases.

More than two-thirds of the patients had a visible and palpable lymph-adenitis, making glandular involvement the commonest form of tuberculosis associated with these tuberculids. In 38 per cent. the adenitis was marked. This very evident association of tuberculids with glandular tuberculosis forms a theoretical basis for explaining their presence in occult cases without visible manifestations. Moreover, the association of tuberculids with a form of tuberculosis that, in a broad way, indicates a high individual resistance to the bacillus is of interesting prognostic significance, and suggests that a tuberculid, among other signs, may be in a way accepted as evidence of a benign course of the disease. This point is of interest in connection with the older conceptions of the extreme gravity of the papulonecrotic tuberculid in infancy. A recent study by Hempelmann has brought forward evidence to show that even in infancy the association with lymphatic tuberculosis (tracheo-bronchial node involvement) can be recognized, and that the prognosis in cases with tuberculids is no graver than in those without.

Among other forms of tuberculosis with which tuberculids in this group were associated the following should be mentioned: sacroiliac abscess, tuberculous peritonitis, renal tuberculosis (bacilli demonstrated) and tuberculosis verrucosa cutis one case each, tuberculous keratitis 3 cases. In one patient the tuberculosis verrucosa cutis occurred on the right leg, the erythema induratum on the calf of the left.



FIG. 9 (171947).—Serpiginous ulcers produced by the confluence of solitary nodules and plaques. Scar of unwarranted surgical interference on the left leg.

*Prevalence of Tuberculids in Connection with Tuberculous Glands.* In endeavoring to ascertain the prevalence of tuberculids in cases of tuberculous adenitis, as observed by internists in the material of a large clinic, 100 cases of tuberculous adenitis were reviewed for evidence that any cutaneous lesion had been observed. In this series 10 per cent. were described as having lesions which could be inferred to be tuberculids. The proportion of men to women among those having cutaneous lesions was as 1 to 10, which is not far removed

from the percentage observed in the series of tuberculids under discussion. There can be little doubt that a number of the less obvious tuberculids were overlooked and that 10 per cent is too small a figure for the incidence of these lesions in glandular tuberculosis.

A careful comparative study of the cutaneous lesions and the types of tuberculous systemic involvement failed to reveal any constant relation between the tuberculous focus and the type of tuberculid. On the other hand, a definite relation between vasomotor and stasis phenomena and the distribution of the tuberculid, was apparent. There was also evidence to show that the more extensive tuber-



FIG. 10 (219380).—Solitary gummatous ulcer with edema and infiltration of the surrounding tissue, to show the differential points.

culids in a rough way were associated with what seemed the more extensive and serious types of systemic tuberculous involvement. Seven of the 9 cases presenting extensive tuberculids involving trunk and extremities also presented the most serious forms of tuberculous involvement in the series.

#### RELATION OF VASOMOTOR PHENOMENA AND VASCULAR STASIS TO THE DISTRIBUTION OF TUBERCULIDS.

It has long been recognized that a tuberculid tends to appear upon the extremities, and especially to appear in those patients in

whom the peripheral circulation is feeble or obstructed. Data on the collateral local vascular findings were collected on 28 cases in this series. Of these one-half (50 per cent.) showed abnormalities of the vascular supply in the form of cyanosis and vasomotor anomalies of the extremities, and swollen hands, legs or feet. Every "stasis leg," that is one with a tendency to passive congestion from defective venous return, had erythema induratum. Five of 7 with blue hands had folliclis. The possession of a leg with a tendency to vascular stasis thus predisposes, to the extent of nearly 100 per cent., to the type of tuberculid known as erythema induratum.



FIG. 11



FIG. 11a

FIG. 11 and 11a (218528).—Erythema induratum with papulonecrotic lesions on the legs of a patient of the "occult" type.

In the same way, the possession of cold, clammy, mottled hands predisposes to the extent of more than 70 per cent., to the development of folliclis. It was a matter of note that all the patients who, at the onset of their cutaneous lesions, had been overweight showed the severest part of their manifestations in the lower extremities; a fact which accords well with the vascular stasis usually present in such legs. Obese persons, therefore, seem to be predisposed to the erythema induratum type of tuberculid, and the thin and neurotic with marked vasomotor imbalance, to folliclis. Only 2 of 7 obese patients had folliclis, and one of these was a child with a generalized tuberculid.

Summarizing the series as a whole from the standpoint of localization of lesions, more than half (57 per cent.) of the patients had lesions on the upper extremities, but almost three-fourths (74 per cent.) had them on the lower extremities, showing the distinct predilection for parts of slower circulation. Ninety-six per cent. of the patients, or practically all, had lesions on either upper or lower extremities. Twenty-three per cent. had lesions on the upper extremities and not on the lower; 43 per cent. on the lower and not on the upper, so that the odds are 2 to 1 in favor of the lower extremity as a site of involvement. One-third had involvement of both extremities, one-third showed involvement of the trunk, and one-fifth of the face. It is of interest to note that 65 per cent. of those in whom the face was involved had lesions on the ears, and that the ear was the seat of lesions in 13 per cent. of the whole series (Fig. 2).

The importance of the circulatory factor in the distribution of tuberculids is one of the strongest arguments for the bacillemic as opposed to the toxemic origin of the process. The presumption is that at points where the circulatory stream is moving most slowly the maximum opportunity for the deposit of organisms will present itself, and that lesions will tend to appear, as they do, in areas where one factor or another acts to delay the movement of the blood.

#### MISCELLANEOUS FINDINGS ON EXAMINATION.

In the study of this series of cases a number of interesting miscellaneous findings developed. The recognition of concomitant tuberculosis in cases exhibiting a tuberculid is, on the whole, a matter of identifying signs by objective examination rather than of eliciting symptoms. Six of the patients had a temperature of 99° or over at the time of examination, although temperature is a much more important factor at onset, especially in those cases which begin as erythema multiforme or erythema nodosum. Of a series of 7 such acute cases, 5 showed temperatures varying from 99° to 103°. Cough had been a well-defined symptom in only 7 of 25 cases, or less than one-third; night-sweats occurred in none, sputum in only 2, both negative for bacilli. On the other hand, amenorrhea was a definite symptom in 43 per cent. of the cases, and in some was coincident with the greatest activity of the tuberculid. Losses of weight, varying from 2 to 45 pounds occurred in 40 per cent., more than half losing less than 10 pounds.

The periodicity of tuberculids and their tendency to exacerbation in spring and fall, which is an important factor in treatment and an aid to diagnosis, were apparent in nearly half of 20 cases in which data were obtained. More than three times as many recurred in spring as in fall, and one-fourth of the patients had lesions continuously.

A little less than half the cases presented secondary anemias with a hemoglobin below 70 per cent. (Dare). In one-fourth of the cases it was below 53 per cent., the lowest being 30 per cent. In the latter case a possibility of a pernicious anemia was entertained. From two of the anemias the influence of syphilis could not be

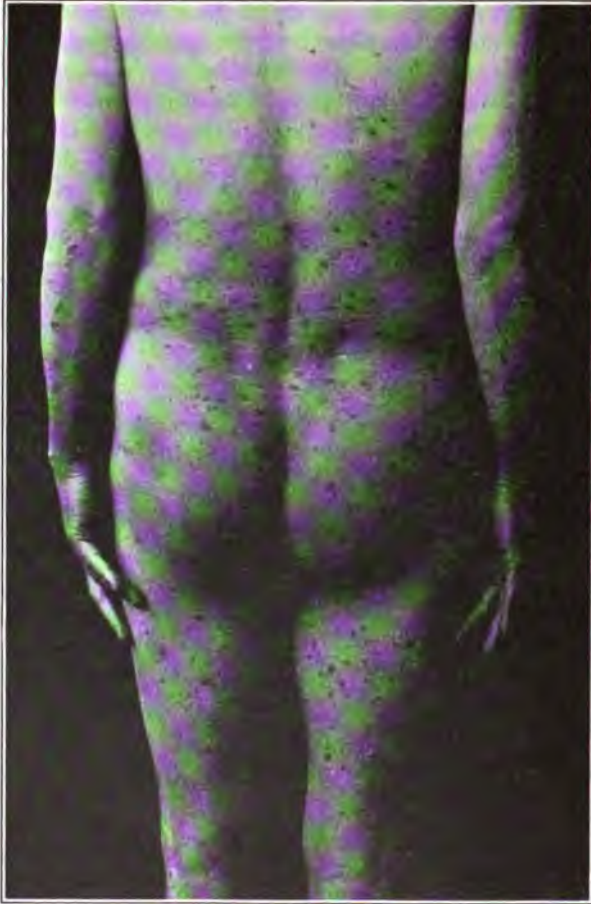


FIG. 12 (226884).—Scars and pigmented residue of acne scrofulosorum, the papulo-necrotic tuberculid of the trunk in a patient with tuberculous adenitis. Note lesions on the extensor surfaces of the forearms also. This patient also had lesions of folliclis on the fingers.

eliminated. Accompanying the anemia was a tendency to leukopenia. Even in the acute cases the patients did not, while febrile, exhibit any tendency to leukocytosis. Thirteen of 25 patients had counts below 6600, 8 below 5800. Only 3 exceeded 10,000. No differential counts were taken. On the score of blood-pressure 35 per cent. were below 120, the lowest 98; 40 per cent. were normal,

and 25 per cent. exceeded 135 systolic, the highest being 142. The higher pressures were all in persons under 31. The diastolic and pulse-pressures exhibited no distinctive variations. Observations on the Wassermann test in the tuberculids will be included in the discussion of allergic manifestations.

It is apparent from this review that the clinical accompaniments of a tuberculid tend to be those of a low-grade tuberculous infection. A moderate secondary anemia and leukopenia with occasionally an afternoon temperature, most likely to appear during exacerbations; moderate loss in weight; occasionally cough associated with a lighting up of the acute process, and signs of a definite but not fulminating process in the lungs or glands make up the average clinical picture in a large percentage of the cases. The florid type of case must constantly be borne in mind in dealing with tuberculids, and mere robustness, weight and color must not be accepted as invalidating a diagnosis based on the tuberculid.

#### THE TUBERCULID IN DIAGNOSIS.

While some caution must be exercised in inferring the diagnostic career of a case from the patient's history or examination, such a study of our series of cases suggested several points of interest. In only 5 of the 30 cases referred for diagnosis to our department had a correct diagnosis been made, and tuberculosis on the score of their cutaneous manifestations had not been suspected. In 2 of the 5 cases the diagnosis might have been made by the internist, but was later made by a dermatologist before the patient was seen by us. In more than one-third of the cases the tuberculid had either been overlooked or ignored as insignificant. This was especially true of acnitis on the face and of folliclis on the fingers. In another third of the cases the cutaneous lesion had been misdiagnosed, to judge from the history or treatment. Six of the 9 cases in this second group had been interpreted as syphilitic, 3 because of the finding of a positive Wassermann, a point to be discussed in connection with allergy. Two were interpreted as luetic because of the history of what was probably a general or extensive shower of tuberculid lesions, of which the scars were present. Another point which seemed to suggest lues was the history of arthritis, myalgia and indefinite pains with mild anemia often given by these patients. Six cases, or one-fifth of the series, had sustained probably needless operative procedures in the effort to make a pathologic diagnosis from the lesions, or for excision, curettage or drainage. The vasomotor and stasis factors had led to a diagnosis of Raynaud's disease in one case, and varicose ulcer in another. One, because of lesions on the elbows, in spite of obvious scars, sustained a diagnosis of psoriasis.

It is apparent that unfamiliarity with the lesions and failure to

observe, whether due to poor light or other cause, together with the tendency to interpret a tuberculid as syphilis, account for four-fifths of the diagnostic errors. For the former difficulty the remedy is obvious. For the latter it should be recalled that not all skin lesions that occur in the presence of a positive Wassermann reaction are syphilitic, and that the recognition of syphilis does not remove



FIG. 13 (234128).—Characteristic scarring and active lesions of the papulonecrotic tuberculid on the elbows of a patient with tuberculous adenitis.

the obligation to ferret out an associated tuberculosis, particularly when the cutaneous evidence points toward it. The occurrence of false positive Wassermann reactions from cholesterinized antigens in the presence of tuberculosis and the absence of syphilis is also being gradually established. The occurrence of tuberculids in crops, their wide distribution upon the face, trunk and extremities, and the frequently associated myalgias and arthralgias are the points in the



history which seem to suggest lues and septic foci rather than obscure tuberculosis to the casual mind. The usefulness of the tuberculid in determining the character of an adenopathy was attested in several cases in which internists had estimated the diagnostic possibilities of cases at 30 to 70 per cent. in favor of Hodgkin's disease, and asked for excisions for diagnosis before seeing the report of the dermatologist.

#### THE COLLATERAL INFECTION FACTOR: ANAMNESIS.

One of the most interesting relations brought out by this clinical study of the tuberculids was that of collateral types of infection shown in the history and in the examination. In the histories of these patients, five syndromes stand out with overwhelming prominence. These are tonsillitis and "rheumatism;" and pneumonia, grippe and pleurisy. The extraordinary prevalence of these two types of infections, representing the focal infections traceable to tonsillar and alveolar pathology and the respiratory group may be seen in Table II. Since the records in these cases were taken by men who had no conception of a possible relationship between the dermatosis and the systemic condition, they are probably quite unprejudiced.

TABLE II.

#### HISTORY OF ACUTE INFECTIONS.

Case.	Tonsillitis.	Rheumatism.	Pneumonia.	Grippe.	Pleurisy.
200229	X	..	..	X	
202732	..	..	..	X	
186129	X	X			
200833	X	..	X	X	X
212370	X	X			
194150	X	X	X	X	
157847	..	..	..	X	
169350	X	X	..	X	X
174923	..	X	X		
39183	..	..	X		
188556	..	..	..	X	
197425	..	X	X	X	
221958	..	..	..	X	
154673	..	..	..	X	
228021	X				
49238	..	X			
224920	X				
228772	X	..	..	X	X
218528	..	..	..	X	X
161592	X	..	X		
191446	X	X			
201284	..	..	..	X	
171947	..	..	..	X	
63167	..	X	X	..	X
230740	..	X			
226884	..	X	X		
233765	..	X	..	X	
234128	..	X			
Total	11 39%	13 46%	8 29%	15 54%	5 18%

Summarizing Table II, it appears that of 28 patients, 39 per cent. had had tonsillitis and 46 per cent. had had rheumatism. Twenty-nine per cent. had had pneumonia, 54 per cent. had had grippe, and 18 per cent. had had pleurisy. Nearly 70 per cent. had had tonsillar infections or rheumatism; 62 per cent. had had definite respiratory infections, not including pleurisy.

TABLE III.

## APPARENT ETIOLOGIC CONNECTIONS.

- Case 186129—Outbreak of general papulonecrotic tuberculid in the spring following a winter of repeated tonsillitis and colds.
- Case 169350—Five years of rheumatoid pains. Grippe followed by pleurisy and abdominal symptoms two years previous to examination; loss of weight, then outbreak of a papulonecrotic tuberculid. No improvement from tonsillectomy.
- Case 154673—Grippe; while recovering, purpura and a papulonecrotic tuberculid.
- Case 188556—"Cold," with temperature, erythema nodosum, marked glandular enlargement on the right side of the neck, signs over right apex.
- Case 197425—Pneumonia 1914, "rheumatism" 1914-1917, then grippe and an outbreak of erythema induratum.
- Case 212370—Tonsillitis, followed by tuberculid, rheumatism, hydrarthrosis, tenosynovitis, tonsils removed without benefit, appendectomy no effect, cleared under treatment for the tuberculid. Teeth negative.
- Case 191446—Folliclis for many years following tuberculous peritonitis. Quinsy three months previous to examination followed by an abrupt outbreak of acnitis in addition to the folliclis. Alveolar abscess.
- Case 230740—Pneumonia 1913, axillary glands then enlarged, removed in 1916, coincidentally with onset of tuberculid.
- Case 174925—Pneumonia sixteen years previously, followed by enlarging glands, removed by operation nine years later. Removal of the glands was followed by severe rheumatism, continuous up to present time. Tuberculid appeared one year after operation; glands recurred.

By the term "rheumatic symptoms" in the foregoing discussion is meant the group of myalgias, neuritides, arthralgias, and occasional arthropathies which do not fall definitely into the category of

acute articular infections. So striking has been the association of this nondescript group of symptoms with the tuberculids that it is now our practice in addition to the routine search for a focus of pyogenic infection in tonsils or teeth, to ray the chests of patients who, in association with suspicious eruptions, complain of "rheumatism."

#### THE COLLATERAL INFECTION FACTOR: FINDINGS.

*Examination of the Tonsils.* Data on the clinical condition of the tonsils were available in 21 cases of the 30. It is to be regretted that



FIG. 14 (228772).—Tuberculid scarring on the elbows.

no pathologic examinations were made in those patients who sustained tonsillectomy while they were under observation. The information derived from clinical examination by an otolaryngologist was briefly as follows:

An exceptional degree of tonsillar infection seemed to prevail in the series as a whole. One-half of the patients were rated as having large and badly infected tonsils. The other half were passable and borderline cases. Practically none were entirely within the limits of normality. On the other hand, curious contradictions seemed to exist in the picture. Almost an inverse ratio appeared to prevail



FIG. 15 (103534).—Scarring about the elbow of a patient with epidermolysis bullosa hereditaria.

between the condition of the tonsil and the severity of the tuberculid. Certainly there was nothing to indicate that the severe tuberculids were directly associated with severe tonsillar infection as seen in purely clinical examination. To confirm this evidence of the absence of direct causal relation between tonsil and tuberculid it appeared moreover, that:

1. The tonsils in patients with tuberculous signs were no worse than in those without. They should have been worse in the latter if they were to play the sole etiologic role.

2. No one tuberculid seemed to bear any special relation to the condition of the tonsils.

3. The tuberculid appeared after tonsillectomy in 3 instances.

4. Tonsillectomy performed in 7 instances failed to prevent or modify the course of the tuberculid.

In the light of these considerations it would appear that there is an indirect relation between infected tonsils and the presence of tuberculids, but no direct relation, both in the history and examination. In other words, the septic tonsil is probably not the tuberculous focus. If it is a factor in the situation, its more probable role is that of a predisposing or contributing factor.

*Examination of the Teeth.* This very important examination was not begun as a routine, unfortunately, until comparatively late in the series, when in studying the clinical picture, the frequent occurrence of a secondary focus became apparent. The results of an examination of 9 cases by x-ray showed alveolar abscesses in 3 and a rarefying osteitis of the alveolar process in one. The presence of definite dental pathology in 45 per cent. of the few patients examined is highly suggestive. It should be emphasized that gross examination of the teeth may afford no clue to the condition beyond the suspicions aroused by dental work which is founded on devitalized teeth. That the alveolar focus is not the leading factor in the production of a tuberculid is again evidenced by the fact that it is not invariably present, and that in two cases in which the teeth were normal to examination and tonsils were out (in one of the two even the appendix was removed) the tuberculid and the accompanying arthritic manifestations, including a tenosynovitis, remained unaltered until the institutions of measures directed against the actual or presumptive tuberculous focus.

It should not be forgotten that the search for a secondary focus in connection with a tuberculid should not terminate with tonsils or teeth. In one of our cases the history and findings suggested an infected gall-bladder as a focus, although the teeth were negative and the tonsils were only moderately involved.

#### THE POSSIBLE BEARING OF CERTAIN ALLERGIC PHENOMENA ON THE ETIOLOGY OF TUBERCULIDS.

Reference was made in the earlier part of this paper to the growth of a body of clinical and experimental evidence in support of an allergic factor in the etiology of tuberculids. As the prime exciter of the cutaneous allergy theoretically necessary to produce the non-specific types of reaction represented by tuberculids, tuberculoxins have been accepted by investigators apparently with wholehearted enthusiasm. Undoubtedly their role is an important if not

the major one. This enthusiasm has for the time being excluded from the field of vision other agents besides tuberculotoxins which are able to excite a non-specific type of cutaneous allergy. For some years the cutaneous allergy of late syphilis (*Umstimmung*), for example, was regarded as highly specific, and the enthusiasm with which luetin was received and used was evidence of this uncritical point of view. It was not until certain observers somewhat more skeptically inclined than the average, such as Boas, began to note the behavior of the skin to controls for luetin, that a field was opened for a non-specific interpretation. Sherrick's observation that the allergy of late lues, as evidenced by reactivity to luetin could be artificially produced by the administration of potassium iodide was a major contribution. In 1916 I argued upon theoretical grounds that the behavior of luetin was not due to the spirochetes which it contained but to an adsorption complex in which agar, the culture medium, probably played a principal role. Acting on the theoretical considerations then presented, I succeeded in showing that agar in proper concentration makes an entirely satisfactory substitute for luetin in the luetin test as applied to late syphilis, and that accordingly the reaction and the allergy on which it depended were alike non-specific. In the course of my study of this phenomenon I was able to demonstrate that an allergy clinically similar to the non-specific allergy of syphilis could be artificially produced by the intradermal injection and lysis of even an autogenous and homologous protein. In this experimental work I employed an emulsion of normal skin, both my own and that of my assistant. As a result apparently of a series of injections of this allergy-producing protein, my assistant and I developed a reactivity to agar which in all respects imitated the allergy of late syphilis. This is essentially an experimental proof of the fact that cutaneous allergy of some types as observed in a disease such as syphilis can be artificially imitated by the intradermal introduction of other proteins than those of the specific organism of the disease. While it is not offered as adequate explanation of the allergic phenomena in tuberculosis as manifested in the development of tuberculids, it is at least suggestive of the idea that proteins other than tuberculo-toxins may be responsible for the allergy that makes tuberculids possible. Such proteins may, in the light of the foregoing clinical observations, be staphylotoxins and streptotoxins, derived from what I have called the secondary focus observed in these cases. It is not impossible that the lysis of such toxins in the body or even of the bacteria themselves in recurrent bacteremias may so sensitize the skin that an embolus of tubercle bacilli will provoke a violent inflammatory reaction of a wholly non-specific character, precisely as agar does in the hypersensitive skin of late syphilis. The allergic specificity of the tuberculin reaction has not as yet been subjected to critical analysis in the light of investigations of the type

detailed above. There are indications that there is a non-specific as well as a specific element in the behavior of tuberculin, not the least of which is Meirowsky's observation, confirmed by Zieler, that the sites of "syphilin" reactions react locally to tuberculin.<sup>7</sup>

The resemblances between the immunologic and allergic phenomena in syphilis and tuberculosis are strengthened by what is still inconclusive but highly suggestive evidence of the lapse in specificity of the Wassermann reaction when tuberculids or tuberculous allergic phenomena are concerned. The present clinical study



FIG. 16 (103534).—Types of scarring on the lower extremities. Epidermolysis bullosa hereditaria—the same patient whose elbows appear in Fig. 15.

and other observations on the behavior of the Wassermann reaction in glandular and occult tuberculosis are gradually accumulating a series of cases in which the presumption against syphilis is so strong that even a positive Wassermann must be guardedly accepted. In this series there were four cases in which positive Wassermans had been obtained, not once but repeatedly. One of the four patients had three weak positive reactions, on the strength of which she had had intermittent treatment for syphilis for a number of years. In three of the cases treatment seemed to secure a reversal

to negative. On the other hand, in three of the cases absolutely no presumptive evidence of an infection has been obtained. Even the therapeutic effects observed are explainable on other grounds. In this connection I recall several cases of tuberculous glands with positive Wassermann reactions, and a case of tuberculous keratitis without evidence of syphilis which cleared up under salvarsan following a single strong positive Wassermann, only to relapse clinically although the Wassermann remained negative. Had these associations in my experience been unsupported in the literature I should have dismissed them as without significance. Jadassohn,



FIG. 17 (174923).—Scarring of a rather large papulonecrotic tuberculid on the calf of the leg. Note the multiplicity of lesions, lack of configuration, peripheral hyperpigmentation. Patient with tuberculous adenitis and arthritic symptoms.

however, refers to Török's observation of positive Wassermanns in association with tuberculids, usually partial positives with one or two antigens. Ravaut, just before the war, had the same experience with several cases in which syphilis could apparently be excluded. Snow and Cooper, as a result of the study of the Wassermann in an army tuberculosis sanitarium, conclude that partial positives in tuberculosis do occur in the absence of syphilis and that they may be due to the cholesterin in cholesterinized antigens. Petroff regards these observations as fully confirmed. My own clinical observations on this point are recorded without further comment, since it is impossible to generalize on so small a group of



cases. In view of these observations it behooves the clinician to give a second thought to the positive Wassermann in association with a tuberculid before accepting it as evidence of syphilis. The caution with reference to the therapeutic test in this connection (p. 325) should also be recalled.

Certain other evidence of an allergic instability in patients with tuberculids appeared in the course of the salvarsan treatment of the patients, and will be discussed in another paper. Of 18 cases on



FIG. 18 (212370).—Hyperpigmentation and scarring due to papulonecrotic lesions on a stasis leg. Patient also had folliclis on the fingers.

which data are available, 9, or 50 per cent., showed varying degrees of idiosyncrasy to arsphenamin or neoarsphenamin. Four reacted acutely, by nitritoid crises on the table, two of them repeatedly. One had a delayed reaction with a toxic erythema, three had gastrointestinal reactions repeatedly and one ran temperatures after injections. This percentage of reactivity enormously exceeds the average observed in patients on the dermatologic service and points to a marked intolerance or instability.

The importance of doing tuberculin reactions in all cases was not appreciated until the evidence of allergic peculiarities began to appear. They were, therefore, done in only 6, by the von Pirquet method. Three active cases were positive and 3 less active cases were negative. The results of tuberculin therapy will be summarized in a subsequent paper. No conclusions should be drawn from the results mentioned here.

*Allergy and the Interpretation of the Secondary Focus in Tuberculids.* It should be understood that no attempt is made to consider either the existence or the importance of a secondary pyogenic focus in cases exhibiting tuberculids, as demonstrated by so small a series as 30 cases. None the less the material studied strongly suggests such a factor. Whether a seemingly pyogenic focal disturbance such as erythema nodosum is a forerunner of tuberculosis as suggested in 1907 by Abt, and as mentioned by Jadassohn in 1915, or merely a follower, remains undecided. It is, of course conceivable on the one hand that a co-existent source of pyogenic infection prepares the soil for tuberculosis much as measles increases the susceptibility to the disease. On the other hand, a tuberculous infection may prepare the soil for the pyogenic. Cases in this series suggest that such extirpation of the pyogenic focus as can be accomplished clinically does not substantially alter the picture so long as the tuberculous focus remains active. The latter is therefore probably the direct etiologic agent. I have suggested theoretical possibilities relating the pyogenic secondary focus to the production of the cutaneous hypersusceptibility which underlies the pathology of a tuberculid in the hope of stimulating experimental study of a possible association between the two as well as further observation on the clinical existence or non-existence of such an entity. A certain amount of clinical evidence for the ability of a focus of pyogenic infection to produce allergic phenomena in the skin in the form of dermatitides and urticarias is apparently accumulating. The subject of the etiologic relation of focal infection to skin diseases is still so completely in its beginnings, however, that clinical observations can hope as yet to have only suggestive value.

#### SUMMARY.

1. The material of this study consists of thirty cases of the so-called papulonecrotic tuberculid, of erythema induratum, and of associated conditions constituting, according to the most widely accepted explanation, the allergic response of a hypersensitized skin to emboli of tubercle bacilli from a tuberculous focus elsewhere in the body.

2. Internists and general diagnosticians should find it worth while to familiarize themselves with the essential lesion of these

types of tuberculids, which may prove of great assistance in the recognition of obscure tuberculosis.

3. The tuberculid when not ignored by the general diagnostician is usually confused as shown by this series, with acne and furunculosis, with syphilis, especially if the Wassermann is positive, and on the legs, with acute surgical conditions and ulcer varicosus. Therapeutic tests for syphilis with arsphenamine are misleading in these cases. The diagnostic import of the lesions in obscure lymphadenitis was at times overlooked.



FIG. 19 (197425).—Scar of a healed ulcer, plaque of erythema induratum on the lower portion of the calf.

4. Association with tuberculosis in this series was evidenced by a family history in one-fourth of the cases, incontestible objective signs in more than half (57 per cent.), and presumptive signs of the disease in 70 per cent. One-third of the patients had radiographic signs of pulmonary tuberculosis; an equal number had suggestive or positive physical signs of lung involvement. The importance of lymphatic involvement is illustrated by the fact that two-thirds of them had a tuberculous lymphadenitis.

5. The type and location of the focus of tuberculosis do not seem to influence the tuberculid beyond the marked association with glandular involvement. On the other hand, the influence of vascular

abnormalities and chronic passive congestion in the extremities is very apparent. Ninety-six per cent. of the lesions involved the extremities. Lesions appeared on the ear in 13 per cent.

6. Slight fever at onset, loss of weight in 40 per cent., amenorrhea in 43 per cent. of the women, moderate leukopenia, slight but occasionally severe anemia, and vernal periodicity are the significant signs. An onset and course marked by rheumatic symptoms is very common (46 per cent.) and often misinterpreted. The recognition of the focus of tuberculosis must depend largely upon objec-



FIG. 20 (218126).—Scar of a noduloulcerative syphilid of the pretibial region. Note the arciform, polycyclic configuration.

tive evidence. There is a notable absence of cough, sweats and hemoptysis. Florid, seemingly robust types of patients are not infrequently subjects of tuberculids.

7. Evidence of the importance of a septic focus and collateral types of infections appears from the history of tonsillitis in 39 per cent., "rheumatism" in 46 per cent., pneumonia in 26 per cent., grippe in 54 per cent. and pleurisy in 18 per cent. These conditions seemed frequently to stand in direct predisposing or exciting relation to the tuberculid. A total of 70 per cent. had symptoms and

findings suggesting the presence of a septic focus, and 62 per cent. had had significant respiratory infections excluding pleurisy.

8. While no direct relation of the tuberculid to the clinical condition of the tonsils could be established, 50 per cent. of the patients had markedly septic tonsils, the remainder were passable, and none were normal.

9. Examination of the teeth by x-ray in a limited number of the later cases demonstrated the presence of septic foci in 45 per cent. of nine patients. Other foci should be searched for.

10. While the secondary or septic focus was obviously present its influence is obscure. Removal of the tonsils in seven cases failed to prevent the outbreak of a tuberculid or modify its course, and complete extirpation of all recognizable septic foci in two cases, without removing or treating the tuberculous focus, was also unavailing.

11. It is conceivable that the effect of a secondary septic focus, while not direct, is predisposing in that toxins or even bacteria, emanating from it may be in part responsible for the cutaneous allergy which is presupposed in explaining the pathogenesis of the papulonecrotic tuberculid. Evidences of the ability of a septic focus to produce or predispose to dermatitis, urticaria and similar expressions of cutaneous hyperirritability are accumulating. Further indirect evidence of a possible peculiar allergic state of patients with tuberculids is found in reported and personally observed cases of non-specificity in their Wassermann reactions and in their hypersusceptibility to arsphenamin.

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### STUDIES IN A CASE OF ACUTE BICHLORIDE OF MERCURY POISONING TREATED BY THE NEWER METHODS, AND FOLLOWED BY RECOVERY.

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1. INTRODUCTION AND REVIEW OF THE LITERATURE. In recent years the treatment of the formerly hopeless cases of bichloride of mercury poisoning has developed along new lines that seem to be of great promise as regards the recovery of these cases.

Lieb and Goodwin<sup>1</sup> emphasized the importance of repeated gastric lavage to remove the mercury excreted into the stomach and Lambert and Patterson<sup>2</sup> have shown the necessity of utilizing every means we have for the purpose of elimination of the mercury from the body. They have shown the necessity of frequent gastric lavage and colon irrigations continued until the washings are free from mercury when tested chemically. Other workers have advised procedures some of which when studied experimentally have failed to protect against mercury poisoning.

Hall<sup>3</sup> recommended the use of a solution of potassium iodide, quinine hydrochloride, hydrochloric acid and water, but Barbour<sup>4</sup> and also Sansum<sup>5</sup> have shown that this antidote is valueless. Fantus<sup>6</sup> has shown that the use of egg albumen is without value unless

<sup>1</sup> Jour. Am. Med. Assn., 1915, lxiv, 2041.

<sup>2</sup> Arch. Int. Med., 1915, xvi, 865.

<sup>3</sup> Jour. Am. Pharm. Assn., 1915, iii, 182.

<sup>4</sup> Jour. Am. Med. Assn., 1915, lxiv, 736.

<sup>5</sup> Jour. Lab. and Clin. Med., 1916, i, 879; 1917, ii, 813.

<sup>6</sup> Ibid., 1918, lxx, 824.

it is given along with or immediately after the poison. He considers lavage with a solution of sodium acetate to be of more value. He also recommends the use of Carter's antidote, a tablet containing 0.36 gram of sodium phosphite and 0.24 gram of sodium acetate. If this is not available he uses a mixture of 5 parts of hydrogen peroxide, 10 parts of water and 1 gram of sodium hypophosphite, using ten times as much hypophosphite as poison and this is followed by copious lavage with the diluted reagent. He also found that sodium bicarbonate had antidotal power, and he uses it in amounts of twenty-five to fifty times the amount of poison taken.

Sabbatani<sup>7</sup> has mentioned the possible value of sulphur, hydrogen sulphide or sodium thiosulphate solutions, as he thinks the use of them as gargles, enemas and hypodermically combat the stomatitis and colitis and impede absorption of the mercury. Linhart<sup>8</sup> advises the use of sodium phosphite as an antidote. Wilms<sup>9</sup> considered that the use of calcium sulphide given by mouth and intravenously was of antidotal power in the treatment of these cases. Hayward and Allen<sup>10</sup> also suggested the use of calcium sulphide. Evans<sup>11</sup> a long time ago considered alkalies of use in the treatment of bichloride of mercury poisoning, and recently Hirsch<sup>12</sup> has suggested the use of sodium bicarbonate as an antidote. Burmeister<sup>13</sup> has emphasized the value of repeated venesections and transfusions in the treatment of these cases. Turrettini<sup>14</sup> reports favorably the use of intravenous injections of glucose solution in mercury poisoning. Carter<sup>15</sup> thinks he has successfully treated these cases by giving by mouth a combination of sodium phosphite and sodium acetate to reduce the mercuric salt to mercurous. Sansum<sup>16</sup> has shown experimentally that this method is without value, and Haskell and Courtney<sup>17</sup> have shown experimentally that the intravenous injection of calcium sulphide is too dangerous a procedure to be of value and that its effect is due to the fluid introduced. Schisler<sup>18</sup> has advised the use of magnesium oxide in these cases. Milian and Saint-Avid<sup>19</sup> advised the use of intravenous injections of alkali and

<sup>7</sup> Biochem. Centralbl., 1906, v, 502; Riforma Med., 1907, xxiii, 767; Arch. Int. de Pharmacol., 1907, xvii, 319.

<sup>8</sup> New York Med. Jour., 1913, xcvii, 1236; Jour. Lab. and Clin. Med., 1917, ii, 722.

<sup>9</sup> Jour. Lab. and Clin. Med., 1917, ii, 445; Lancet-Clinic, 1915, cxiv, 555; 1916, cxv, 460; Ther. Digest, 1916, xi, 71.

<sup>10</sup> Jour. Am. Med. Assn., 1913, lx, 1827.

<sup>11</sup> Med. and Phys. Jour., London, 1800, iii, 535.

<sup>12</sup> Chicago Med. Rec., 1914, xxxvi, 444.

<sup>13</sup> Jour. Lab. and Clin. Med., 1917, ii, 500.

<sup>14</sup> Rev. Med. de la Suisse romande, 1915, xxxv, 204.

<sup>15</sup> Chicago Med. Record, 1914, xxxvi, 444; Critic and Guide, 1915, xviii, 266; Am. Jour. Clin. Med., 1914, xxi, 314.

<sup>16</sup> Jour. Am. Med. Assn., 1918, lxx, 824.

<sup>17</sup> Jour. Lab. and Clin. Med., 1917, iii, 110.

<sup>18</sup> Jour. Mississippi Med. Assn., 1917, xiv, 173.

<sup>19</sup> Paris méd., 1917, vii, 213.

glucose. Holm<sup>20</sup> advised the use of calcium sulphide. Macnider,<sup>21</sup> from his studies on the protection that alkalies give to the development of tubular nephritis in uranium poisoning, advises the use of alkalies in acute mercury poisoning. He found that death in acute bichloride of mercury poisoning in dogs was due to shock associated with a mercury enteritis and to delayed kidney damage associated with acidosis. He thought that the delayed kidney injury was not due to the action of mercury as such during its elimination by this organ. Anderson<sup>22</sup> advised water irrigations through a cecostomy wound to hasten the bowel elimination in these cases. Weiss<sup>23</sup> has published a method for treating these cases somewhat similar to that described by Lambert and Patterson, with the exception that the frequent gastric and colonic lavage is omitted. One improvement in his method over that of Lambert and Patterson is that the urine is kept alkaline to a saturated solution of methyl red in alcohol, on the basis that Fischer has shown that if the urine of a nephritic cannot be made alkaline to methyl red this patient continues in a dangerous state.

There is no doubt that the treatment of cases of acute bichloride of mercury poisoning by the newer methods has produced better results than by the former treatment, which was really watching the case until fatal anuria developed. Schisler<sup>24</sup> reports 16 cases with 5 deaths, dose from 3 to 170 grains. Weiss<sup>25</sup> reports 28 cases with 1 death, dose from 3 to 82 grains, the cases being treated by the newer methods.

Brown and Baskett,<sup>26</sup> Lewis and Rivers,<sup>27</sup> and Cohen and Bernhard<sup>28</sup> have reported cases with recovery following the Lambert-Patterson treatment. Nolan<sup>29</sup> has recently presented a very able review of recent work in regard to acute mercuric chloride poisoning. It should be recalled that in the elaboration of any method of treatment of bichloride of mercury poisoning the following conditions are to be met:

The development of anuria, which occurs in from twelve hours up to ten days after taking the poison, due to an acute nephritis and enteritis, and the colitis, due to the inflammation caused by excretion of the mercury into the intestine. Together with this there exists an acid intoxication, and, as Nolan well says: "The therapeutic problems are (1) to reduce the toxicity of the mercury

<sup>20</sup> Jour. Michigan State Med. Soc., 1917, xvi, 270.

<sup>21</sup> Jour. Med. Research, 1912, xxi, 79; Jour. Exper. Med., 1918, xxvii, 519; 1916, xxiii, 171.

<sup>22</sup> Surg., Gynec. and Obst., 1915, xx, 350; Harrold: Ann. Surg., 1916, lxiii, 127.

<sup>23</sup> Jour. Am. Med. Assn., 1917, lxviii, 1618.

<sup>24</sup> Jour. Mississippi Med. Assn., 1917, xiv, 173.

<sup>25</sup> Ohio State Med. Jour., 1917, xiii, 595; Jour. Am. Med. Assn., 1917, lxviii, 1618.

<sup>26</sup> Jour. Am. Med. Assn., 1917, lxviii, 1622.

<sup>27</sup> Johns Hopkins Hosp. Bull., 1916, xxvii, 193.

<sup>28</sup> Jour. Am. Med. Assn., 1916, lxvii, 1019.

<sup>29</sup> Interstate Med. Jour., 1917, xxiv, 997.



in the system; (2) if possible to hasten its elimination; (3) to combat the acid intoxication and its attendant evils.

That some method to facilitate the elimination of the mercury present in the body is needed is shown by the following data. In a case of bichloride of mercury poisoning in which death followed ten days after taking the drug I<sup>30</sup> was able to find the following amounts of mercury still present in the body:

Organ.	Mercury present in milligrams.
Kidney . . . . .	5.8
Spleen . . . . .	1.7
Liver . . . . .	39.82
Brain . . . . .	1.68
Stomach . . . . .	1.50
Small intestines . . . . .	4.80
Large intestines . . . . .	7.28
Heart . . . . .	5.81
Lungs . . . . .	trace
Blood . . . . .	52.2
Muscle . . . . .	25.8
Bile . . . . .	trace
Stomach contents . . . . .	12.2
Intestinal contents . . . . .	8.6
Rectal contents . . . . .	8.4

Some recent experimental work of Sansum<sup>31</sup> seems to show that when an amount of mercuric chloride in excess of 4 mg. has entered the tissues at large, death regularly occurs, and that we have no adequate grounds for believing that death is preventable by any known form of treatment. He thinks that therapeutic efforts should be directed toward the mechanical removal of the poison from the lumen of the alimentary tract and antidoting the poison before it leaves the portal circuit—that is, particularly before absorption. However, Sansum does not take into consideration the treatment of the acidosis present in these cases.

2. CASE HISTORY. A man, aged thirty-five years, physically well but mentally sick, chewed up three 7½-grain tablets of bichloride of mercury at twelve o'clock noon. He vomited at two o'clock, and the vomitus contained streaks of blood. He was given, at three o'clock, the whites of three eggs and a quart of milk, and this was vomited in ten minutes. The treatment outlined in this paper was started at seven o'clock—that is, seven hours after the poison was taken. During the first two days the bowels moved every two or three hours and the movements contained shreds of mucus and blood. The stomach washings also showed clumps of clotted blood during this time; a severe stomatitis developed on the third day. Excruciating lumbar pain came on during the second day and lasted for three days. At the end of the first week I felt confident that the patient would recover. He was carefully watched for one month

<sup>30</sup> Rosenbloom: Jour. Biol. Chem., 1915, xx, 123.

<sup>31</sup> Jour. Am. Med. Assn., 1918, lxx, 824.

and was discharged as completely recovered. He is at present (twelve months after his illness) well in all respects and no trace of damage to his kidneys can be found by examining his urine or by testing the kidneys by the functional methods.

The following tables contain the data obtained in the study of this case of acute bichloride of mercury poisoning:

TABLE I.—ANALYSES OF BLOOD.

Day.	Total non-protein nitrogen. Mgm. per 100 c.c. blood.	Urea nitrogen. Mgm. per 100 c.c. blood.
1	42	20
2	48	25
3	84	66
5	140	94
8	172	140
10	176	138
12	141	100
14	92	70
17	60	40
20	48	25
22	40	20
24	36	18
25	32	12
28	28	11
30	23	10

3. LABORATORY STUDIES. Foster,<sup>32</sup> Phillip,<sup>33</sup> Myers and Lough,<sup>34</sup> Squier and Myers,<sup>35</sup> Campbell and Hunter,<sup>36</sup> Woods,<sup>37</sup> and Lewis and Rivers<sup>38</sup> have published chemical studies of the blood in bichloride of mercury cases. When my results are compared with those obtained by these observers it may be noted that at no time did the blood non-protein nitrogen or urea-nitrogen reach the high values found by some of these workers. I consider that the lower values obtained in this case were due to the better excretion by the kidney, owing to the treatment used. However, there is a marked increase in the non-protein nitrogen and the urea-nitrogen of the blood in acute bichloride of mercury poisoning.

DISCUSSION OF TABLE II. The presence of large amounts of acetone and diacetic acid in the urine with the high ammonia nitrogen points to the existence of a definite acidosis. That an acidosis exists in uremia was shown long ago by von Jaksch.<sup>39</sup> Straub and Schlayer,<sup>40</sup> Sellards,<sup>41</sup> Palmer and Henderson,<sup>42</sup> How-

<sup>32</sup> Arch. Int. Med., 1915, xv, 755.

<sup>33</sup> Med. Klinik, 1913, ix, 912.

<sup>34</sup> Arch. Int. Med., 1915, xvi, 536.

<sup>35</sup> Jour. Urol., 1918, ii, 1.

<sup>36</sup> Jour. Biol. Chem., 1917, xxxii, 195; 1918, xxxiii, 169; Arch. Int. Med., 1917, xx, 919.

<sup>37</sup> Arch. Int. Med., 1915, xvi, 577.

<sup>38</sup> Johns Hopkins Hosp. Bull., 1916, xxvii, 193.

<sup>39</sup> Ztschr. f. klin. Med., 1889, xiii, 350.

<sup>40</sup> München. med. Wchnschr., 1912, lix, 569.

<sup>41</sup> Johns Hopkins Hosp. Bull., 1914, xxv, 141.

<sup>42</sup> Arch. Int. Med., 1915, xvi, 109.

land and Marriott<sup>43</sup> and Peabody<sup>44</sup> have also found an acidosis present in uremia. However, this case shows that there was an overproduction of acid bodies and that the acidosis was not entirely due to an imperfect excretion of the acid radicals, as is claimed by Palmer and Henderson. The existence of this acidosis shows the necessity of treating cases of bichloride of mercury poisoning with this factor in mind. It shows the necessity of using the low protein, low fat and high carbohydrate diet and the use of alkalies to keep the urine persistently alkaline to methyl red. It may be noted that on the twenty-fourth day of the illness all damage to the kidney had been repaired, as evidenced by changes in the urine. From this day on the urine was normal in all respects. The acidosis was kept under control by the use of alkalies, glucose and high carbohydrate, low protein and low fat diet. I think that the control of the acidosis was an important feature in the successful outcome of this case.

TABLE II.—ANALYSES OF THE URINE.

Day	Volume, c.c.	Sp. gr.	Reaction.	Protein gm. per liter.	Nitrogen gm.	Ammonia nitrogen.		Acetone.	Di-acetic acid.	Microscopic.				
						Gm.	Per cent. of total Nitrogen.			Hyaline casts.	Granular casts.	Red blood cells	White blood cells	Epithelial cells.
1	300	1010	Acid	3.5	3.8	0.22	6.0	xxxx	xxxx	xx	xx	xx	xx	xxx
2	420	1008	Acid	4.0	3.9	0.23	5.8	xxxx	xxxx	xx	xx	xx	xx	xx
3	880	1009	Acid	4.0	5.2	0.53	10.2	xxxx	xxxx	xx	xx	xx	x	xx
4	1800	1010	Acid	1.0	6.2	0.90	14.5	xxxx	xxxx	xx	xx	xx	x	xx
5	3000	1012	Acid	1.0	7.1	0.89	12.6	xxxx	xxxx	xx	xx	xx	x	xx
6	4200	1010	Alkaline	0.5	8.1	0.73	8.9	xxxx	xxxx	xx	xx	xx	x	xx
7	4800	1010		0.5	7.2	0.91	12.7	xxx	xxx	xx	xx	xx	x	xx
8	6000	1010	"	0.5	10.4	1.00	9.6	xxx	xxx	x	x	xx	x	xx
9	6400	1012	"	Trace	11.6	1.03	8.9	xx	xx	x	x	xx	x	x
10	5200	1010	"	"	10.8	0.93	8.6	xx	xx	x	x	xx	0	x
11	5000	1009	"	"	9.7	0.78	8.1	xx	xx	x	x	x	0	x
12	4840	1010	"	0.5	10.2	0.82	8.0	xx	xx	x	x	x	0	x
13	3200	1012	"	0.5	10.3	0.77	7.5	x	xx	x	x	x	0	x
14	3000	1014	"	Trace	9.8	0.72	7.4	x	x	x	x	x	0	x
15	1500	1015	"	"	9.4	0.61	6.5	x	x	x	x	x	0	x
16	1420	1018	"	"	8.6	0.53	6.2	x	x	x	x	x	0	x
17	1400	1016	"	"	7.2	0.44	6.1	0	0	x	x	x	0	0
18	1200	1015	"	"	6.8	0.35	5.1	0	0	x	x	x	0	0
19	1100	1010	"	"	7.4	0.39	5.3	0	0	x	x	x	0	0
20	1000	1018	"	"	7.2	0.36	5.0	0	0	x	x	x	0	0
21	1860	1012	"	"	7.0	0.41	5.8	0	0	x	x	x	0	0
22	1500	1012	"	0	6.8	0.32	4.7	0	0	x	x	x	0	0
23	1450	1014	"	0	5.6	0.25	4.5	0	0	x	x	x	0	0
24	1860	1010	"	0	5.8	0.29	5.0	0	0	0	0	0	0	0
25	1010	1018	"	0	7.2	0.37	5.1	0	0	0	0	0	0	0
26	1200	1015	Acid	0	7.1	0.37	5.2	0	0	0	0	0	0	0
27	1280	1018		0	8.6	0.55	4.6	0	0	0	0	0	0	0
28	1400	1017	"	0	8.4	0.40	4.8	0	0	0	0	0	0	0
29	1030	1014	"	0	7.6	0.34	4.5	0	0	0	0	0	0	0
30	1200	1018	"	0	7.2	0.32	4.4	0	0	0	0	0	0	0

<sup>43</sup> Johns Hopkins Hosp. Bull., 1916, xxvii, 63.<sup>44</sup> Arch. Int. Med., 1914, xiv, 236; 1915, xvi, 955.

TABLE III.—PHENOLSULPHONEPHTHALEIN TEST.

Day.	Per cent. of dye excreted in the First hour.	Second hour.	Total.
1	trace	trace	
2	trace	trace	
3	5	5	10
5	10	5	15
8	15	10	25
10	18	12	30
12	20	15	35
14	18	18	36
17	20	18	38
20	25	20	45
22	30	20	50
24	35	20	55
25	35	15	50
28	40	20	60
30	40	20	60

DISCUSSION OF TABLE III. This table shows very nicely the damage done to the kidneys by the bichloride of mercury and the gradual resumption of the kidney function in the later days of the illness. From the merest trace of the dye being excreted on the first and second days following the ingestion of the mercury, the amount gradually increased until on the twenty-second day it could almost be considered normal and on the twenty-eighth day the excretion of the dye was normal.

TABLE IV.—STUDIES OF THE MERCURY EXCRETED.

Day.	Urine.	Mercury present in:	
		Colon washings.	Gastric washings.
1	xxxx	xxxx	xxxx
2	xxx	xxx	xxx
3	xxx	xxx	xxx
5	xxx	xxx	xxx
8	xxx	xxx	xxx
10	xxx	xx	xx
12	xx	x	x
14	x	x	x
17	x	x	x
20	x	x	x
22	Trace	Faint trace	Faint trace
24	Faint	" "	" "
25	"	Very faint	Absent
28	Absent	Absent	"
30	"	"	"

DISCUSSION OF TABLE IV. The necessity of continuing the treatment of these cases for a long period of time is clearly shown by a study of this table. Fairly distinct amounts of mercury were still present in the urine, colon washings and gastric washings for a period of twenty days following the ingestion of the mercury. Faint traces were still present up until the twenty-eighth day. There is no doubt that the best method is to continue the treatment used in these cases until the urine, the colon washings and the gastric washings are free from mercury.

The method of treatment that was used in this case was a combination of various procedures that have been advised for the treatment of mercury poisoning. It may be tabulated as follows: In this case the sodium phosphite and sodium acetate were not used, instead the hypophosphite-peroxide mixture was used.

#### METHOD OF TREATMENT TO BE USED IN CASES OF BICHLORIDE OF MERCURY POISONING.

1. Administer the whites of three eggs beaten up in a quart of milk and then empty the stomach by siphonage.
2. Give 300 c.c. of fresh calcium sulphide solution, containing 1 grain to 1 ounce of water by mouth.
3. Wash out the stomach with fresh calcium sulphide solution, 1 grain to 1 ounce of water.
4. Administer in powder or tablet 0.36 gram of sodium phosphite and 0.24 gram of sodium acetate. If this is not available give the following:

Sodium hypophosphite . . . . .	1 gram
Water . . . . .	10 mls.
Hydrogen peroxide . . . . .	5 mls.

Use ten times as much of the hypophosphite as poison taken. Give a copious lavage of stomach with the above antidote diluted twenty times. Give the above undiluted antidote every eight hours for two days.

5. Pour through the stomach tube after the above lavage a solution of 3 ounces of sodium sulphate and 6 ounces of water containing 5 grains of calcium sulphide. Let these solutions remain in the stomach.

6. Give intravenously after withdrawing 600 c.c. of blood, 800 c.c. of Fischer's solution or of bicarbonate-glucose solution.

7. Wash out the stomach morning and night, giving by the mouth after each washing, 5 grains of calcium sulphide dissolved in 3 ounces of water. Continue this lavage until the stomach washings are free from mercury when tested by Elliott's<sup>45</sup> method and until the urine is free from mercury.

8. Give high colon irrigations of warm water morning and night, using 8 gallons of the water for each treatment.

9. Give a hot pack twice daily.

10. Give 8 ounces of milk every second hour.

11. Give every second hour 8 ounces of the following solution, by mouth, alternating with the milk:

Potassium bitartrate . . . . .	dr. j
Sodium citrate . . . . .	dr. j
Sucrose . . . . .	dr. j
Lactose . . . . .	dr. iv
Lemon juice . . . . .	oz. j
Boiled water . . . . .	oz. xvj

<sup>45</sup> Jour. Am. Med. Assn., 1917, lxviii, 1693.

12. Force the patient to drink large quantities of the alkaline waters, such as Celestin's Vichy or Kalak water.

13. Give a low fat and low protein and high carbohydrate diet for four weeks. Avoid salt in food, as it increases the absorption of the mercury.

14. Give by continuous proctoclysis a solution containing 1 dram potassium acetate, 4 drams glucose and 3 drams sodium bicarbonate to the pint.

15. Keep the urine alkaline to methyl red.

16. Continue rest of treatment until recovery, usually a period of three weeks.

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### A CASE OF BULIMIA, WITH REMARKS ON THE CAUSAL TREATMENT OF SOME FUNCTIONAL DISEASES.<sup>1</sup>

BY GEORGE DOCK, M.D.,

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THOUGH bulimia is always mentioned in the proper connection, it rarely gets into indexes, and does not seem to be very frequent in practice. The descriptions in text-books are as a rule very good, but the tendency to place bulimia with polyphagia in diabetes or exophthalmic goitre must raise doubt in the mind of anyone who sees a case like the one I report, or even one who reads a current definition, as to its place in pathology. Recent studies of hunger, especially those of Cannon and Carlson and their collaborators, give an added interest to all anomalies of hunger. For these reasons and on account of the outcome of the case, I report the history of a patient sent me recently for investigation.

G. S., aged thirty-six years, architect.

*Diagnosis.* Bulimia, pansinusitis, acute rhinitis, pharyngitis and laryngotracheitis, caries of teeth, alveolar abscess.

*Complaint.* The patient has to eat more frequently and in larger quantities than normal. Hunger attacks begin with general feeling of uneasiness, followed, if food is not taken, by an intense headache, generally in the eyes or frontal region. Sometimes headache comes quickly if food is not taken, sometimes it is delayed. The patient eats from five to fifteen times in twenty-four hours. More accurately, he has no regular meal time and does not always eat with the family, but eats at any time he feels a craving. At family meals he may take a bowl of soup, crackers, rice or bread. He has acquired the habit of eating toasted bread cubes, which he always has with him in large tin cans. He will eat a bowlful of these, or five to eight shredded wheat biscuits each time he gets hungry.

<sup>1</sup> Read before the Association of American Physicians, Atlantic City, May 7, 1918.

*Family History.* Mother and two sisters died of cancer of stomach. Father and one sister living and well. No history of tuberculosis, arthritis, constitutional or nervous disease.

*Previous History.* As an infant, patient had digestive disorders, according to a statement from his mother, and up to seven years had an idiosyncrasy to bananas. From seven to twenty-one he was always well. About twenty-one, while at college, he overworked, and at one time was ill two weeks with "gastritis and pleurisy." He lost weight from 175 to 135 pounds. There were then recurring attacks, following fatigue or overwork, but gradually becoming less frequent. These attacks began with a chill, followed by abdominal distention, pain through the chest, radiating to the back, causing the patient to double up. There were eructations, which seem to have suggested the name "gastritis" for the attacks. After the last attack, five years ago, the patient followed a diet composed of easily digested food. At the age of twenty-two the right arm became paralyzed and remained so for two years, but gradually recovered. The cause was not clearly made out, though the patient was examined by several distinguished neurologists. The final opinion expressed was that the paralysis was due to sleeping on the arm.

In February, 1918, he had an infection in the head, spoken of as "grip," since which time the nose has been obstructed. The patient seemed to have been almost wholly free from subjective symptoms, and had no severe sinusitis symptoms. Later, he gave a history of "catarrh," for which the nose was treated when he was sixteen. Since then he has kept the nose clear by snuffing up salt solution. He had no idea the condition was severe and was not aware of his nasal voice. He had always led an active life, riding and walking much, playing tennis, association football and hockey. No abuse of alcohol. No history of venereal disease.

The present trouble (voracious appetite) dates from January, 1915. At first he felt hungry about 9 P.M., and would eat a bowl of rice or something similar. The condition gradually grew more severe.

Three years ago he weighed 145 pounds. He now weighs 215 pounds. In the last six weeks he has grown short of breath. When the amount of food is large the bowels are loose.

The hands have not become larger. Does not think there is any change in shape or size of head.

The present diet has been described. The amount of water consumed varies with the food, but is always more than normal. The amount of urine seems increased, but has not been measured.

The patient has been under the care of various physicians. Recently, under the view of a ductless gland disease, he was treated in turn with dried thyroid, adrenalin and pituitary preparations. The first had no effect, but the others seemed to give relief and reduced the appetite. Had also taken tincture of belladonna up to

20-drop doses. The throat got very dry and the symptoms were checked for about a day, but returned. Patient has washed out his stomach with a tube, daily for a week, with benefit. He found that bulky vegetables relieved hunger longer than meat. He can eat all kinds of food. Sometimes a small amount of food satisfies; at times he cannot eat enough.

*Physical Examination* (February 9, 1918). Man of large, heavy frame, well formed. Panniculus moderately thick; no abnormal fat distribution.

The skin is warm, pink or mottled when stripped in a rather cool room. Patient does not object to the cold. The lips and finger tips are slightly cyanotic. The abdomen shows white lines from the pressure of the bedclothes. Nail scratch brings out white lines, remaining several minutes. Gentle stroke with finger brings out broad white line, also lasting several minutes. The scalp hair is thin in front. Eyebrows and beard (shaved) heavy. Body hair scanty; semifeminine escutcheon.

The supra-orbital prominence, malars, nose and chin of good size, but not pathological. The voice is nasal obstructive; the nose is obstructed and shows pus in the anterior nares. The teeth are well shaped, unusually regular and not spaced. Five molar teeth are decayed to the roots. The other molars and the bicuspid are extensively repaired, but show several cavities. The gums are swollen and reveal exudate in several places. The patient explained the bad condition of his mouth by saying he could not abstain from eating long enough to let a dentist work on him.

The tongue is not large. The posterior wall of the pharynx is covered with tenacious yellow mucopus.

The thyroid is not palpable.

Thorax broad, deep and symmetrical. Expansion good. Auscultation and percussion of lungs negative.

The heart-impulse is not visible or palpable. Dulness extends 11 cm. to the left in the fifth interspace,  $2\frac{1}{2}$  cm. to the right in the third, 2 cm. in the fourth. The first sound at the apex is impure. There is a soft blowing systolic murmur in the aortic area. Aortic second sound accentuated. The radial pulse is of good volume. Blood-pressure, 188 to 92.

The abdomen is above the level of the ribs, the wall thick and firm. Liver and spleen not palpable.

The right arm is smaller than the left, 30.5 cm. as compared with 31.5 cm. at the insertion of the deltoid. Both forearms equal; right grip weak, the thumb and index only being affected by the weakness, but with little atrophy. The right hand is paler than the left.

The reflexes are normal.

Some small hemorrhoids, otherwise rectal examination negative.

Blood: Hemoglobin, 90; red blood corpuscles, 6,600,000; leukocytes, 5600.



Wassermann tests, blood and spinal fluid negative. Five cells per cubic millimeter in the spinal fluid. Ross Jones negative.

Urine: Admission specimen, clear, light yellow. Specific gravity, 1010; acid; no sugar; no albumin. Phenolsulphonethalein test, 10 min. trace; 1 h. 10 min., 25; 2 h. 10 min., 22; total, 47 per cent.

Blood chemistry, February 9: Non-protein nitrogen, 30.1 mg. per 100 c.c. Urea, 13.2 mg. Sugar, 0.0495 gm. per 100 c.c.

Examination of stomach contents: Vomitus on passing tube; about 200 c.c.; semisolid; no mucus; no blood; HCl, 24; total acidity, 46. No lactic acid. No bacilli, yeasts or sarcines. Fat and starch present.

Test-meal, shredded wheat biscuit: Free HCl,  $\frac{1}{2}$  h., 35; 1 h., 20;  $1\frac{1}{2}$  h., 20; 2 h., 35;  $2\frac{1}{2}$  h., 30; 3 h., 25. Total acidity,  $\frac{1}{2}$  h., 55; 1 h., 60;  $1\frac{1}{2}$  h., 45; 2 h., 55;  $2\frac{1}{2}$  h., 40; 3 h., 40.

Stool: (February 9), 410 grams, formed, dry. Large amount of shredded wheat biscuit like coarse bran; no mucus, blood or pus.

The first night the patient was in the hospital orders were left to give him anything he asked for. Between 8 P.M. and 6 A.M. he took 800 c.c. of milk; 5000 c.c. of water and 16 shredded wheat biscuits, besides some bread cubes; calories, 1684. The next twenty-four hours he took total calories, 7038.4.

These quantities of food were not considered excessive by the patient. They were lessened by the further examinations, so that we had no opportunity for seeing the possibilities in that way.

February 10. The blood examination gave non-protein nitrogen, 25 mg. per 100 c.c.; urea, 16 mg. per 100 c.c. Blood-pressure, 160 to 90. White line as before.

Sugar tolerance in blood tests: before test, 0.087;  $\frac{1}{2}$  h. after, 200 grams glucose, 0.170; 1 h., 0.115;  $1\frac{1}{2}$  h., 0.105; 2 h., .97;  $2\frac{1}{2}$  h., .95. No sugar in urine at any time.

#### URINARY CONDITIONS DURING OBSERVATIONS.

February 9 . . . . .	Amount	3800 N	9.98 NH <sub>4</sub> N	0.863
" 10 . . . . .	"	4645 N	16.29 NH <sub>4</sub> N	1.98
" 11 . . . . .	"	2900 N	16.40 NH <sub>4</sub> N	2.01
" 12 . . . . .	"	2400 N	14.61 NH <sub>4</sub> N	1.90
" 13 . . . . .	"	1800 N	14.37 NH <sub>4</sub> N	1.78

Skiagram of head, stereoscopic, shows large frontal sinuses; posterior half of skull very thick, especially inner plate. Sella small, shallow. Appearance as of bridge of bone across top.

Films of teeth show periapical infection of two teeth and suspicious areas around several others. Referred to dentist.

Examination of nose and throat by Dr. C. A. Gundelach, February 11: Left nasal chamber entirely occluded by several polyps. Right chamber filled with pus. Evident middle and superior meatus suppuration. Nasopharynx greatly infected; pharynx also. Tonsils

small; submerged; chronic tonsillitis. Lingual tonsil considerably hypertrophied. Larynx and trachea show acute inflammation.

February 11. Roentgen-ray examination, gastro-intestinal, by Dr. R. W. Mills (abstract): Stomach rather atonic; is large in all dimensions; gastric tonus fairly good only; pyloric tonus fairly good. Gastric motility no more rapid or slower than normal. No initial clearance. Cap perfect; ring perfect. At four and three-quarter hours stomach empty. Barium in terminal ileum and ascending colon. Barium enema shows cecum and entire colon of rather large dimensions; takes one-third more enema than usual. No definite evidence of colonic hypermotility. No abnormalities in or about appendix.

The patient became restless while the various tests that prohibited eating were carried on. It soon became clear that diabetes and organic stomach disease, intestinal disease and intestinal parasites and pancreatic disease could be ruled out. Pituitary disease and disease of the central nervous system seemed possible to exclude, also neurasthenia and hysteria.

The condition of the teeth and the nose and accessory cavities indicated something more than symptomatic treatment. The character of the food eaten between meals made one think of relief to reflex irritation, and the mouth and nose seemed possible sites of such irritation. I therefore advised the patient to have the local diseases treated at once, stating that this might stop the chief symptoms; if not, further investigations into metabolism were agreed to by the patient.

Work on the mouth was begun by Dr. Wm. B. Spotts, dentist in the medical service, and on the nose by Dr. Gundelach. The hopelessly defective teeth were extracted and the infections treated. The nasal polyps were removed, the largest three-quarter inch in diameter. Both antra were opened nasally and all the sphenoidal and ethmoidal sinuses and large quantities of foul pus washed out.

By March 5 the patient reported himself very much improved. "He eats three times a day, and though sometimes hungry is much less so than before. He looks well, but his voice is still somewhat nasal."

April 4. Nose almost well. No voracious appetite for a month, except once, and then not bad. No hunger at night. Feels much better in every way. Weight, 190 pounds. No white line, only a red line fading rather rapidly.

May 1. Feels well. Weight, 185 pounds. Large appetite only once since last visit; none at night.

There was no opportunity to make observations such as Carlson made with such advantage with intragastric balloons, so that we cannot tell the details of the hunger contractions. But it seems certain from the roentgen rays as well as the clinical observations that rapid emptying of the stomach had nothing to do with the

hunger pain. Attractive as this theory of bulimia is, it seems that it must be an infrequent explanation, from negative evidence. In patients with cancer of the cardiac end of the stomach, with rapid, sometimes instantaneous emptying, hunger has not been present. My roentgenologic colleague, Dr. R. W. Mills, tells me he has not seen it in any of some 25 cases of rapid emptying after gastro-enterostomy.

It is perhaps going too far to assert that the treatment was the cause of the improvement. Many will think the condition was a neurosis and the improvement a coincidence, perhaps only temporary. However that may be, I think the case has a lesson in showing the advantage of treating local diseases that may cause functional disorders rather than resorting to the narcotics, depressants or other symptomatic remedies still recommended and used in such cases.

The case illustrates another feature of therapeutics. For years medical teachers have emphasized the importance of "treating the patient and not the disease," of ascertaining the complete anatomical and functional condition of the patient and correcting all anomalies. This would seem to mean that all morbid processes should be treated, instead of treating abstract conceptions.

Focal infections, sometimes causing local symptoms, always capable of setting up other and dangerous processes, would seem to indicate careful and exhaustive treatment. And yet we see all kinds of neuroses in patients with infections of the teeth, tonsils, prostates, or appendices, but little or nothing done with the demonstrated foci unless a haphazard effort with vaccines.

### A STUDY OF MIGRAINE.

BY MARY P. S. RUPERT, M.D.,

AND

ELIZABETH E. WILSON,

PHILADELPHIA.

AN eminent English neurologist has said: "There is no problem that requires more thorough and searching investigation than the origin of headaches, and there is no condition so unimportant that it can be overlooked in any case of headache."

With the above axiom in mind, the work on the study of migraine was undertaken—to find the origin of the disturbance, and if possible to correct it. In a condition so varied, the lines presenting for investigation are indeed numerous, and, we believe, none are too trifling to be passed by.

Migraine is the commonest of all forms of headache. This is hardly disputable by anyone who takes the trouble carefully to investigate the history. On the whole, more women than men are attacked—the proportion about 6 to 4—and social status seems to exert very little influence, as one finds the condition as frequently in the poor as in the idle rich. On the other hand, it is probable that brain workers in consequence of their mode of life are more frequently and severely visited than those whose business is in the open air.

The symptoms begin usually in childhood. In individual cases, however, the condition makes its appearance only in the third or fourth decade. If the onset is given with certainty as late as this, the diagnosis should be made with caution.

There are few ills which depend to the same degree as migraine upon direct homogeneous heredity. Moebius, indeed, found that 90 per cent. of his cases showed direct heredity. This point is of great theoretical and practical interest.

The predisposition to hemicrania must be distinguished from the exciting causes of the outbreaks, and frequently the first attack follows one of the infectious diseases, typhoid, scarlet fever, influenza and the like. Among the actual exciting causes of individual attacks are: emotional disturbances, anger, any mental over-exertion and alcohol. Constipation and menstruation play a very important role. It is a fact that disease of the mucous membrane of the nose and accessory cavities and of the ears, as well as irregularities of the eyes, will precipitate attacks. Migraine not uncommonly accompanies a patient throughout life, although with considerable intermissions.

This condition so prevalent among us has been known since the time of Hippocrates, and derives its name from the Greek word, which means hemicrania. It was so named by Galen.

In contradistinction to the word *hemicrania*, the pain is not necessarily so limited, and, indeed, in certain cases of migraine there is no headache at all.

Migraine is not a disease entity, but rather a symptom-complex occurring in various forms and intensity in different people.

In order to provide a background, we shall use a modification of the classification as given by Flatau.

1. **MIGRAINUS VULGARIS.** This is a frequent form, accompanied by pressure in the head, lassitude, anorexia and nausea. The eye symptoms and actual pain may or may not be present. This type rarely has an aura.

2. **OPHTHALMIC TYPE.** The symptoms are legion, but the striking and ever-present few which may make the diagnosis for the doctor when seeing the patient are: sensitiveness to light and noises, with scotoma scintillans; exquisite pain in the head, not necessarily limited to a hemicrania, but felt over the entire head,

with aching in the jaws, the nose and the occiput region. This type is accompanied by nausea and vomiting and great prostration during the attack. Paralysis of individual ocular muscles sometimes occurs during the attack, with some resulting ptosis.

3. **VASOMOTOR TYPE.** This has, if possible, more symptoms to its credit than the ophthalmic variety, and among them may be included: hemicrania, or diffuse pain; angioneurotic edema; abdominal pain; disturbances of peristalsis; cardiac depression; breathlessness; yawning or sneezing, with marked dizziness.

4. **PSYCHICAL MIGRAINE.** Psychical migraine differs from the vulgaris type in that it has marked psychical disturbances within physiological limits, such as temporary loss of memory, temporary aphasia, hysterical spasm, garrulousness and melancholia.

Pathology has shown no demonstrable lesion; therefore, the cause has been the subject of innumerable speculations. It may be readily understood how such varied symptoms in so many parts of the body lead to varied hypotheses. It would seem to us the theories most worthy of mention are:

*The Reflex Theory.* This is based upon the idea that the condition is produced by a reflex stimulation of some important organ, such as the uterus, eye, nose, stomach and the like.

*The Vasomotor Theory.* The vasomotor theory depends upon the vasomotor processes and upon arterial hyperemia. In this theory certain groups of symptoms are explained also by venous or passive congestion, while still others are to be accounted for by weakened functional control. These changes may cause marked vascular contractions or the so-called angiospastic form.

*The Central Theory.* The central theory would prove the process as primarily in the brain substance, the principal factors being hyperemia or congestion of the brain cortex and meninges. Spritzer suggests that an excessive secretion of the choroid plexus is associated with either a functional or anatomical stenosis (partial or complete) of the foramen of Monro and a subsequent congestion of the brain. Deyl believes a swelling of the hypophysis to be the underlying factor. Quinke holds that an angioneurosis causes increased brain-pressure and Schulke introduces the colloid theory in attempting to account for too much brain substance for the skull capacity. However interesting these points may be they are entirely hypothetical, and careful histological-anatomical examinations have not confirmed them.

*The Toxic Theory.* The toxic theory presupposes some disturbance of metabolism, and most frequently mentioned is gout in its so-called neuroarthritic form, or a disturbance of the endocrine system, or a combination of both.

**ANALYSIS.** Consideration of all these views leads to the conclusion that the symptoms of migraine arise from stimulation of certain areas in the central nervous system and that this stimu-

lation may be provoked in many ways: by pressure, by reflex stimulation or by circulation in the blood of certain toxic materials, the nature of which has not been satisfactorily determined.

It is with the last named that our studies have been chiefly concerned. With this factor in view we have tried to find a possible source of poison.

Case No.	Age.	Heredity.	Age at onset.	Frequency of attacks.	Possible contributory factors.
1	38 years	Migraine; carcinoma	20 years	Every three or four weeks	Chronic tonsillitis.
2	24 years	Negative	22 years	Two or three times a week	Astigmatism.
3	56 years	Negative	18 years	Every two or four weeks	Pyorrhea and dental caries; cholelithiasis (operation three years ago); eye trouble. Artificial menopause.
4	32 years	Syphilis; tuberculosis	18 years	Every two weeks	Pyorrhea.
5	45 years	Negative	20 years	Every ten days	Pyorrhea.
6	48 years	Tuberculosis	25 years	Once a week	Cervical lymphangitis.
7	36 years	Negative	14 years	Once in two weeks	pyorrhea.
8	40 years	Carcinoma	33 years	Once a week	Goitre; cholelithiasis (operation one year ago); pyorrhea.
9	33 years	Rheumatism; chorea	26 years	Once or twice a week	Spur in nose.
10	22 years	Tuberculosis	Childhood	Irregular, associated with unusual mental strain	Astigmatism and strabismus.

Case No.	Wassermann.	Blood count.	Routine urinalysis.				Blood-pressure.	
			Sp. gr.	Albumin	Casts.	Indican.	Systolic.	Diastolic
1	Negative	Normal	1021	—	+	+	100	74
2	Negative	Normal	1030	—	—	—	92	62
3	Negative	Normal	1027	—	+	+	176	93
4	Negative	Normal	1011	—	—	—	101	65
5	Negative	Normal	1032	+	—	+	116	72
6	Negative	Normal	1021	+	—	+	120	75
7	Negative	Normal	1012	—	—	—	100	70
8	Negative	Normal	1015	—	—	—	113	69
9	Negative	Normal	1015	+	+	—	113	68
10	Negative	Normal	1013	+	—	—	118	72

In each case a careful study has been made of the gastric contents and the feces. The problem of nitrogen retention was studied by the quantitative estimation of urea in the blood, and the kidney function was investigated by the tests which have been accepted as most dependable, *i. e.*, the phthalein and the Mosenthal test diet.

To eliminate other possible factors and to round out a complete study of the case we have included the Wassermann test, the blood count and routine urinalysis. A careful history has been taken of each patient and a thorough physical examination made in a search for predisposition and for an exciting cause.

In the course of the physical examination we have noted that many cases of migraine run an abnormally high blood-pressure

during the attack; therefore, we have made a careful study of this particular phase of the subject, estimating the blood-pressure both during and between the attacks.

It has been interesting as well as significant to find that each case having frequent and severe attacks of migraine shows, then, *some abnormality of the stool, usually putrefaction, with an alternation of blood-pressure, and these are usually accompanied by delay of kidney function with some disturbance of nitrogen output.*

Case No.	Specific gravity, range.	Examination of												Result.	Blood urea.
		Fluids.				Chlorides.				Nitrogen.					
						Day.		Night.		Day.		Night.			
		Day.	Night.	Total.	Result.	Grams.	Per cent.	Grams.	Per cent.	Grams.	Per cent.	Grams.	Per cent.		
1	23	864	170	1034	Normal	9.67	1.16	1.68	0.90	4.95	0.55	2.38	1.40	Normal	85
2	8	1448	620	2068	Poor	7.30	0.50	1.90	0.30	11.60	0.80	3.00	1.30	Poor	890
3	8	1074	670	1744	Fair	5.47	0.50	3.90	0.58	12.00	1.10	0.13	0.20	Poor	240
4	14	1140	640	1780	Fair	3.30	0.29	2.04	0.32	5.01	0.44	4.16	0.65	Poor	160
5	23	804	620	1424	Poor	5.50	0.69	1.98	0.32	5.64	0.70	6.01	0.97	Fair	120
6	17	1178	580	1758	Normal	5.30	0.44	2.61	0.45	6.60	1.70	6.50	0.90	Normal	119
7	6	902	603	1532	Poor	9.49	0.78	1.60	0.39	5.23	0.80	3.21	0.51	Fair	300
8	6	1378	550	1928	Poor	6.33	0.46	1.18	4.96	4.96	0.36	1.76	0.32	Poor	280
9	18	1086	722	1808	Normal	4.67	0.40	3.82	0.40	3.69	0.34	2.02	0.28	Normal	310
10	13	680	692	1372	Poor	4.48	0.65	3.80	0.54	3.73	0.54	4.13	0.59	Poor	230

Case No.	Renal function. Phenolsulphonaphthalein test.			Gastric contents.	Feces.	Results.
	1st hour.	2d hour.	Total.			
1	18.0	8.5	26.5	Hyperacidity (mild)	Putrefaction	Improved.
2	14.0	15.5	29.5	Normal	Putrefaction	Improved.
3	21.0	16.5	37.5	Normal	Putrefaction	Improved.
4	14.0	8.0	22.0	Normal	Putrefaction	Improved.
5	22.0	17.5	39.5	Normal	Putrefaction	Improved.
6	27.5	13.5	41.0	Normal	Acid fermentation	Improved.
7	28.0	15.5	43.5	Hypersecretion	Putrefaction	Improved.
8	11.0	10.5	21.5	Normal	Putrefaction	Not improved.
9	41.0	15.5	56.5	Normal	Putrefaction	Improved.
10	14.5	12.5	27.0	Normal	Acid fermentation	Not treated.

Our own clinical observations confirm those of other investigators who find unusually high blood-pressure readings during the attack and varying blood-pressure readings in the intervals of the attack, either high or low.

We have further found that this variation of blood-pressure between attacks corresponds with the findings in the stool. For instance, a persistently low blood-pressure reading is apt to be associated with an excessively putrefactive movement, and as the stool condition is corrected, the attacks are less in frequency and

severity, and some cases show improvement in pressure between attacks.

What, then, is the source of the irritation? Our next work on this will be an attempt to find the possible toxin—whether or not it is a chemical poison contained in the putrefactive stool.

We propose from now on to investigate in each case the abnormal chemical elements in the stool with reference to the blood-pressure findings and the kidney retention; and while still feeling that the problem of each case is an individual one, we are hoping that some useful suggestions for treatment in general may be derived from our further work.

The laboratory work was done in the laboratory of the Woman's Hospital of Philadelphia, under the direction of Dr. Berta O. Meine, director of the laboratory.

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## TWO CASES OF GAUCHER'S DISEASE IN ADULTS: A STUDY OF THE HISTOPATHOLOGY, BIOLOGY AND CHEMICAL FINDINGS.

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Up to the year 1916 only nineteen cases of Gaucher's disease had been reported in which the diagnosis was established by histological examination. An abstract of these cases may be found in a paper on the subject by Mandlebaum and Downey in the *Folia Hematologica*, February, 1916. Since that time the available literature reveals but two authentic cases. The first, reported by Dr. Frank A. Evans, May, 1916, occurred in a boy four years and eleven months of age with a history of splenic enlargement beginning at the age of two years, accompanied by frequent attacks of epistaxis. The histological examination of the spleen and other hemopoietic organs is typical of Gaucher's disease. The second case was described by Dr. Mark S. Reuben, January, 1918. The patient, a boy, aged two years, presented the clinical picture of Gaucher's disease, and an examination of the splenic pulp removed by aspiration revealed the characteristic cells. As a rule, clinicians are opposed to probatory puncture in cases of splenic hypertrophy on account of the danger of hemorrhage, but the diagnosis in suspected cases of Gaucher's disease may always be established if the typical cells are found in the aspirated fluid. This diagnostic procedure was employed for the first time in Gaucher's disease by Bernstein who found the characteristic cells just before splenectomy, the diagnosis being corroborated subsequently by histological examination of the spleen.

The cases reported by Knox, Wahl and Schmeisser in January,



1916, as Gaucher's disease, have no resemblance whatever to that disease and should not have been classified as such. The reasons for excluding these cases from the group under consideration have been published by Downey and the writer. Two cases of splenic hypertrophy occurring in sisters, five and seven years of age, respectively, were reported in March, 1917, by De Lange and Schippers as probable instances of Gaucher's disease, despite the fact that the pathological examination of both spleens removed at operation showed a total absence of the large cells and other characteristic features of that disease. One year later the authors again described the same cases, stating frankly that their original interpretation was incorrect and also admitting their inability to classify the cases.<sup>1</sup>

On account of the infrequency of Gaucher's disease and the uncertainty in the minds of some authors regarding its pathology a further attempt to establish the disease on a firm anatomical basis will be made. In the following report of two cases recently observed and studied, some disputed questions relating to the histogenesis of the large cells found in the hemopoietic organs will be discussed, also the chemical nature of the substance present in these cells.

The clinical and diagnostic features of the disease have been described so often in previous papers that it appears unnecessary to present them in detail at this time, excepting to state that the disease usually begins in infancy or childhood and is characterized by a progressive enlargement of the spleen and subsequently of the liver, a discoloration of the skin of the exposed parts of the body, a peculiar thickening of the conjunctivæ, a tendency to hemorrhages, such as epistaxis or bleeding from the gums, and a definite leukopenia. The superficial lymph nodes are not enlarged, jaundice does not occur and ascites is rare. The disease is distinctly chronic and terminates as the result of a complicating affection. The organs involved are the spleen, liver, lymph nodes and bone-marrow, the distinctive feature being the presence in each of these organs of large cells showing a peculiar type of cytoplasm not exactly duplicated in any other pathologic condition.

CASE I.—The patient, a married woman, aged forty-one years, a native of Austria, was admitted to the Mount Sinai Hospital, service of Dr. Morris Manges,<sup>2</sup> November 16, 1915. The family history is negative; no brothers or sisters had any similar disease. The patient is the mother of three children. An operation had been performed at the Presbyterian Hospital in August, 1908, for an abscess of the anterior abdominal wall just below the umbilicus. At that time the spleen, which had been enlarged since an attack of

<sup>1</sup> A discussion of alleged cases of Gaucher's disease reported prior to 1913 and not substantiated by microscopic examination may be found in the paper by Brill and Mandlebaum.

<sup>2</sup> To Dr. Manges and to Dr. Lilienthal, who subsequently operated upon the patient, I am greatly indebted for the privilege of using their clinical records.

malaria in her sixth year, extended from below the tip of the tenth rib on the left side to 4.5 cm. to the right of the umbilicus, and seemed to descend into the pelvis. The surface was smooth and hard; the left border could not be determined. Both legs were covered with black and bluish spots, the patient was poorly nourished and anemic and the temperature occasionally rose to 102°. Blood examination at this time showed 3,200,000 red cells, 2000 leukocytes, hemoglobin, 80 per cent. A later count showed 5000 leukocytes, polymorphonuclears 53 per cent., lymphocytes 47 per cent., hemoglobin 50 per cent. Polychromatophilia was noted and six normoblasts and one megaloblast were seen in a count of 300 leukocytes. The patient was discharged, after five weeks, with the diagnosis of chronic interstitial splenitis.

On admission to Mount Sinai Hospital the patient complained of pain in the left hypochondrium and precordial region, cough, night-sweats, fever of four weeks' duration and blood-tinged sputum for one day. She had lost more than twenty pounds in weight in the course of ten years. The physical examination revealed, in addition to systolic heart murmurs at the apex and over the aortic area, an enormously enlarged and movable spleen reaching into the pelvis. The hand can be placed between the spleen and the costal margin and a notch felt high up. The edge is rounded, the surface smooth; no tenderness. The liver extends from the fifth intercostal space obliquely downward into the right iliac fossa; the edge is thin and sharp, the surface smooth, hard and tender. A pale brownish discoloration of the skin of the face is noted, especially on the forehead; the entire abdomen shows a brown pigmentation, also the lower extremities. In some places, chiefly above the malleoli, the color is brownish black, and on the thighs numerous rounded spots, brown in color and one-half inch in diameter, are seen. Some of the lesions on the legs are evidently the result of hemorrhagic pustules. The superficial lymph nodes are not appreciably enlarged, but a few nodes can be felt in both axillary regions. There is no thickening of the conjunctiva, but a few minute petechiæ seen in both eyes disappeared after four days. For a few days a positive reaction for blood was obtained in the semifluid stools. At this time the hemoglobin was 54 per cent.; red cells, 2,720,000; leukocytes, 2600; polymorphonuclears, 58 per cent.; lymphocytes, 38 per cent.; mononuclears, 4 per cent.; normoblasts, 4 per cent. Subsequently 5 megaloblasts were seen in making a count of 100 leukocytes and poikilocytosis and polychromatophilia noted; one month later myelocytes, 5 per cent., were counted. An examination of the blood for total cholesterol showed 0.11 per cent. The Wassermann reaction was negative. At this time the patient had a severe epistaxis and several attacks followed during the next week. Bone tenderness over the sternum and ribs was also noted. On January 30, 1916, the hemoglobin was 48 per cent.; red cells, 2,688,000;

leukocytes, 1400. The general condition remained about the same and the patient left the hospital a week later. The discharge diagnosis made by Dr. Manges was: "Splenomegaly, Gaucher type."

The patient was readmitted on March 2, 1916, complaining of dragging pains in both legs. The physical examination shows marked pulsation in the suprasternal notch, mitral and aortic murmurs, a huge spleen and liver, intense skin pigmentation and palpable lymph nodes in both inguinal regions and axillæ. The blood examination shows hemoglobin, 60 per cent.; red cells, 4,720,000; leukocytes, 2800; polymorphonuclears, 34 per cent.; lymphocytes, 60 per cent.; mononuclears, 6 per cent. Anisocytosis, poikilocytosis and basophilic stippling are noted.

On March 14 a lymph node was excised from the right axilla and submitted to me for histological examination. The report was: "Chronic fibrosis. A few large reticular phagocytic cells filled with pigment are present. These have a similarity as far as shape and size are concerned to the large cells found in Gaucher's disease. A positive diagnosis cannot be made. The axillary nodes in the reported cases of Gaucher's disease frequently contain but few large characteristic cells." The blood at this time showed a total cholesterolin of 0.0875 per cent.<sup>3</sup> The patient refused to be operated upon and left the hospital on April 6, 1916.

She returned to the hospital May 1, 1916, with no pronounced changes in her general condition, and a splenectomy was performed by Dr. Howard Lilienthal on May 29, 1916. A twelve-inch longitudinal incision was made from one inch below the xiphoid to one and one-half inches above the os pubis and a six-inch oblique incision running into the left hypochondriac region at an angle of 75 degrees from the first incision. The spleen occupied the entire left side of the abdomen and part of the right, covering the left lobe of the liver and a portion of the right lobe. The liver was markedly ptosed so that its lower border occupied part of the pelvis. The spleen was easily removed, the entire operation lasting thirty-seven minutes. Immediately afterward a transfusion was performed, the patient receiving 400 c.c. of blood. The postoperative history was uneventful and the patient was out of bed on the ninth day. On the day of operation the blood showed hemoglobin, 55 per cent.; red cells, 2,200,000; leukocytes, 12,000; polymorphonuclears, 62 per cent.; lymphocytes, 36 per cent.; mononuclears, 2 per cent. After transfusion the hemoglobin was 60 per cent.; red cells, 2,420,000; leuko-

<sup>3</sup> The cholesterolin content of the blood in many affections of the spleen or liver, especially when accompanied by non-obstructive icterus, such as Banti's disease, pernicious anemia and some forms of splenomegaly with blood changes, is either normal, or decidedly less than normal, in amount. Such is the case in Gaucher's disease. After splenectomy the cholesterolin content is always elevated for a certain period, but returns slowly to normal. No particular clinical value can be attached to these findings in Gaucher's disease, on account of the limited number of observations.

cytes, 13,600; polymorphonuclears, 90 per cent.; lymphocytes, 10 per cent.; many normoblasts and megaloblasts. The blood picture was practically unchanged while the patient remained in the hospital and a moderate leukocytosis of from 7000 to 21,000 persisted, with a fairly normal ratio of lymphocytes to polymorphonuclears. The patient gained thirteen pounds in weight and was discharged on July 4, 1916.

**HISTOLOGICAL EXAMINATION.** The spleen directly after removal weighs 4250 grams (nine pounds six ounces) and measures 38 cm. in the long axis; width at upper pole 16 cm., at lower pole 21 cm., average thickness 9 cm. The general appearance is that of an

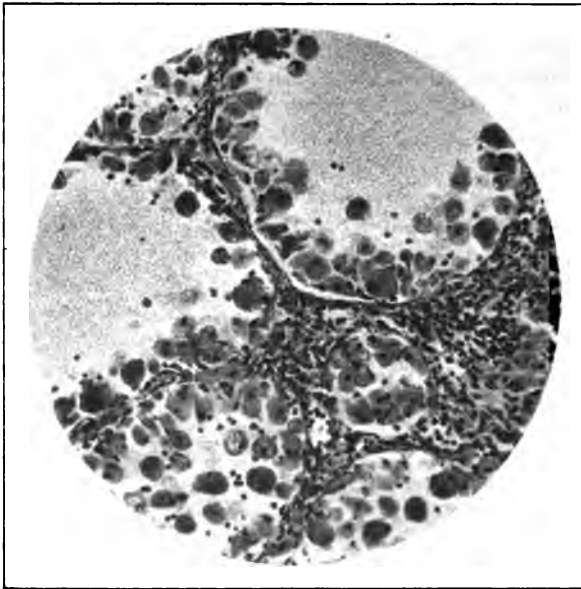


FIG. 1.—Section of spleen. In upper field are two dilated venous sinuses containing large cells and red blood cells. Alveoli filled with large cells are seen below, also collections of normal pulp cells.  $\times 400$ .

enormously hypertrophied spleen with a well-marked notch. The large vessels are greatly dilated but appear normal otherwise. One small lymph node is seen at the hilus. The surface is dark purplish in color, but a cut section shows a somewhat brownish hue. Very minute yellowish dots are seen on the cut surface, also small hemorrhagic areas with yellowish markings. These areas protrude slightly above the cut surface and have an average diameter of 0.5 cm. A few red infarcts of small size are also noted. There is no apparent increase of connective tissue. Stained smears made from the freshly cut surface show numerous large, multinucleated cells characteristic of Gaucher's disease.

Frozen sections were made at once from the fresh spleen and stained with Sudan III and Nile blue, but no trace of fat or lipid substances could be found. Examination of frozen sections with the polariscope failed to show any anisotropic bodies.

Blocks of tissue were preserved in alcohol, Zenker's solution, formalin and Helly's fluid, and the sections stained by a large variety of methods. The sections show the typical picture so often described in the genuine cases of Gaucher's disease. The pulp is almost entirely replaced by large, round or oval, alveolar spaces containing the characteristic cells. Many of these spaces are dilated venous sinuses bounded by a narrow band of connective tissue and partially lined with flattened endothelial cells. In addition to the large cells one also sees numerous red blood cells. Other alveoli contain only large cells and are bounded by delicate connective-tissue septa with no endothelial lining (Fig. 1). Many adjoining sinuses communicate with each other and in some situations the wall is broken and the sinus communicates directly with the pulp. The Malpighian bodies are diminished in number and those present are moderately hypertrophied. Small collections of normal pulp cells are crowded between the dilated sinuses. A small amount of bright yellow pigment is found in the sections. This is in form of minute crystals lying free or contained in small reticular cells. The pigment gives a positive reaction for iron. There is no positive evidence in these sections that the Gaucher cells are phagocytic for erythrocytes. A few multinuclear cells resembling megakaryocytes are seen here and there.

Although an examination for the presence of fat or lipoids had been made on frozen sections of fresh spleen with a negative result, as mentioned above, additional polariscopic and microchemical tests were made on frozen sections of the tissue fixed in formalin. These tests were uniformly negative, confirming the statement repeatedly made that lipid substances cannot be found in the Gaucher cells by microchemical methods.

Sections of the small lymph node found at the hilus of the spleen present the typical picture described in this disease and show a moderately advanced involvement. Large cells are seen in considerable number, but the lymph-adenoid tissue is only partially replaced by these cells. The individual follicles are still clearly outlined, principally those near the cortex, and no marked activity is seen in the germinal centers. The sinuses are moderately dilated and contain lymphocytes, erythrocytes and pigmented cells. The pigment is both crystalline and amorphous in character, of a brownish-yellow color and is seen along the trabeculae, in the fixed cells of the reticulum and in the sinuses. Only a small number of pigment granules give a positive reaction for iron, the crystalline form being negative.

From this brief description of the spleen and lymph node it may

be seen that the histopathology is typical of Gaucher's disease. In order to avoid repetition the structural details of the large cells will be described later in connection with a consideration of their origin and nature.<sup>4</sup>

CASE II.—The patient, male, aged thirty-seven years, a native of this country, was admitted to Mount Sinai Hospital, service of Dr. A. A. Berg,<sup>5</sup> January 14, 1918. Both parents and several brothers died of causes unknown to the patient; one brother alive and well. At the age of twenty-five he consulted a physician for diffuse abdominal pain and was told that "something was beginning to grow" in his abdomen. The pain ceased soon afterward, and he experienced no further abdominal symptoms for ten years. Then he noticed a gradual enlargement of the abdomen, accompanied by a dragging sensation. The only other complaint was frequent attacks of epistaxis, at times profuse in character. Four months before admission he began to have sharp pains in the left hypochondrium, radiating to the shoulder and extending over the entire abdomen. The heavy, dragging sensation persisted. No history of fever or loss of weight.

The physical examination on admission reveals a well-developed though slightly emaciated man with a markedly protuberant abdomen. The spleen is greatly hypertrophied; the lower pole felt midway between the umbilicus and the left anterior superior spine. A distinct notch is felt a few inches below the costal margin, the edge is sharp, the surface smooth, not tender, and the organ moves freely with respiration. The liver is not apparently enlarged and cannot be palpated. A distinct fluid wave is elicited in the abdomen. The skin of the face is somewhat dark in color and many brownish colored patches and scars are seen on the legs. The superficial lymph nodes are not distinctly enlarged, but a few soft nodes are palpable in the axillæ. A distinct conjunctival thickening is present in each eye on both sides of the cornea. The Wassermann reaction is negative. The blood on examination shows hemoglobin, 35 per cent.; red cells, 3,500,000; leukocytes, 9000; polymorphonuclears, 52 per cent.; lymphocytes, 46 per cent.; mononuclears, 2 per cent. Poikilocytosis and anisocytosis are noted, but no nucleated erythro-

<sup>4</sup> The patient again entered the hospital on April 5, 1918 (two years after the splenectomy), complaining of pain in the right thigh and loss in weight. Her general condition had improved after the operation, the epistaxis had not returned, the pain in the legs disappeared and she gained in weight. On admission it was noted that the skin pigmentation was less prominent and of lighter color. The cervical, axillary and inguinal lymph nodes are small but palpable. The liver extends from the upper border of the fifth rib to 15 cm. below the costal margin; surface and edge slightly irregular. Some tenderness of long bones and sternum noted. Hemoglobin 68 per cent., red cells 3,600,000, leukocytes 7500, polymorphonuclears 55 per cent., lymphocytes 36 per cent., mononuclears 6 per cent., transitionals 2 per cent., eosinophiles 1 per cent., a few normoblasts. Total cholesterolin 0.194 per cent.

<sup>5</sup> I am deeply indebted to Dr. Berg for his kindness in permitting me to study this case and for the use of the clinical data.

cytes are seen. Examination for total cholesterin shows 0.108 per cent.

Both Dr. Brill and the writer, who were asked to examine the patient, concurred in the diagnosis of Gaucher's disease.

Five days after admission a splenectomy was performed by Dr. Berg. A long transverse incision was made parallel to the lower edge of the ribs from the midline downward and outward as far as the costovertebral angle, and upon opening the abdomen more than a liter of bloody fluid escaped. Many dense adhesions were found between the spleen and omentum, prolonging the time of operation. Drainage of the wound was made. A blood transfusion of 600 c.c. was then performed and the patient reacted satisfactorily. On the following day the blood showed hemoglobin, 50 per cent.; red cells, 3,776,000; leukocytes, 28,800; polymorphonuclears, 80 per cent.; lymphocytes, 17 per cent.; mononuclears, 3 per cent.; many normoblasts but no megaloblasts. Two days later the blood picture was practically the same but the leukocyte count fell to 23,600. For ten days the patient's condition remained satisfactory, then the temperature rose to 105° following a chill, and a considerable amount of serous fluid escaped from the drainage opening. The patient's condition from this time became steadily worse, and two days later the original wound opened spontaneously. This was again sutured, but the patient continued to have high temperature, and died February 6, 1918. Examination of blood for total cholesterin four days before death showed 0.132 per cent.

**HISTOLOGICAL EXAMINATION.** The spleen immediately after removal weighs 3500 grams (seven pounds eleven ounces) and measures 25 x 18 x 12.5 cm. The general configuration of the organ is retained. There are four notches on the anterior border and two on the posterior border. A number of large omental adhesions are seen in the neighborhood of the hilus. The surface is smooth but marked by numerous small, globular elevations which project slightly above the surface. These correspond to small hemorrhagic areas seen upon cross-section of the organ. The color on section is grayish or purplish brown, the consistency firm, the surface rather smooth but dotted with innumerable semitranslucent areas measuring about 1 mm. in diameter. A number of rounded hemorrhagic areas with central necrosis are seen on the cut surface, varying from 1 to 4 cm. in diameter. The Malpighian bodies cannot be recognized. At the hilus a few dark red lymph nodes are seen. These measure from 0.5 to 2 cm. in diameter.

Smears made from a freshly cut surface show many characteristic large cells with multiple nuclei. Frozen sections were made from the fresh spleen and stained with Sudan III and Nile blue, but no lipid substances or fat could be found. Polariscopic examination for double refracting substances was also negative. The histological picture as seen in paraffin sections is almost identical

with that described in the previous case, and therefore requires no detailed description. Microchemical tests for fat or lipoids made on frozen sections of the spleen fixed in formalin were uniformly negative. A small amount of pigment is seen in the trabeculae and in the walls of the larger bloodvessels.

**POSTMORTEM EXAMINATION.** This was performed five hours after death by Dr. William Thalhimer. The body is that of a poorly nourished man, with a peculiar brownish color of the skin. Numerous dark brown, circular areas of pigmentation are seen on both legs. A long incision in the left hypochondrium extends from below the free border of the ribs in the median line downward and outward to the costovertebral angle.

**Heart:** Normal.

**Lungs:** Normal in size and appearance; crepitation throughout; several firm, dark areas 1 to 2 cm. in size just below the pleura.

**Thymus:** Fatty remains only are present.

**Tracheobronchial lymph nodes:** Considerably enlarged, soft, pinkish color on section, succulent.

**Abdomen:** About 500 c.c. thin, bloody fluid present. Peritoneal surfaces smooth and glistening everywhere. The splenic vessels are ligated with heavy silk and are in good condition. A thin layer of fibrin is seen in this region, but no other exudate is found.

**Liver:** Weight, 2040 grams; right lobe measures 23 x 19 x 10.5 cm.; left lobe, 17 x 14 x 4.5 cm. The surface presents a peculiar grayish-brown color; slightly increased resistance to knife on section; cut surface is pale, succulent and broken up into small islands by increased connective tissue. Nearly all of the radicals of the portal vein are completely filled with slightly adherent mixed thrombi, red and white. The portal vein is completely filled by a recent dark red, slightly mixed, adherent thrombus, lamellated in places and very soft. The thrombus extends up the portal vein into all its radicals and down into the splenic vein, which is completely filled as far as its ligated end. It extends down as far as the openings of the large mesenteric veins into the portal, but does not extend into the mesenteric veins proper. The gall-bladder is somewhat enlarged, densely adherent to the transverse mesocolon, causing a slight constriction of the duodenum and contains one small rounded calculus. The bile ducts appear normal.

**Kidneys:** Normal size, capsules not adherent, surface pale and smooth; on section, somewhat cloudy.

**Adrenals:** Slightly smaller than normal; medulla, dark brown in color.

**Esophagus:** Normal.

**Stomach:** Enormously distended with gas. The veins contain no thrombi; mucosa, hemorrhagic in places.

**Intestines:** Mucosa of duodenum studded with small, bright red, hemorrhagic areas; same condition present in entire length of small



and large intestine; mucosa slightly edematous; lymphoid follicles and Peyer's patches normal in size and appearance.

**Abdominal lymph nodes:** Mesenteric and retroperitoneal lymph nodes enlarged to about twice the normal size; soft, succulent, pinkish color on section. A small calcareous deposit is seen in one mesenteric node.

**Pancreas:** Normal.

**Bone marrow of vertebræ:** Dark red in color, soft in consistency.

**HISTOLOGICAL EXAMINATION.** Blocks of all the organs removed were fixed in a large variety of fluids and paraffin sections were studied.

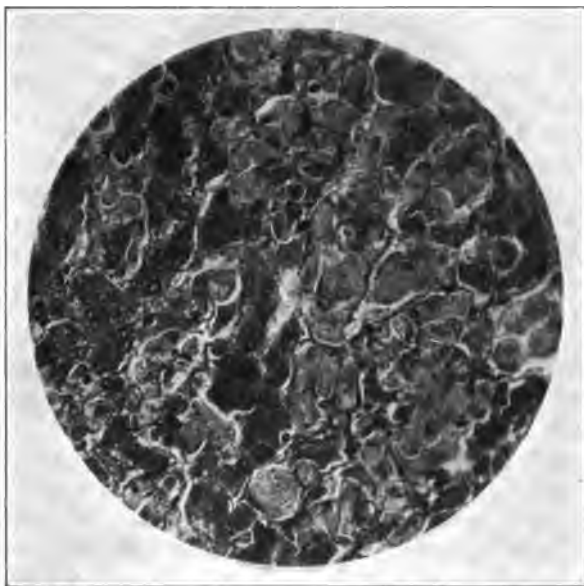


FIG. 2.—Section of liver. Large cells in the interlobular connective-tissue spaces on the right. Columns of normal liver cells on the left, also large cells in the sinusoids.  $\times 400$ .

**Liver:** Although this organ is not enlarged, contrary to the rule in cases of Gaucher's disease, the picture is typical. With low magnification one sees an enormous increase of interstitial connective tissue, giving the appearance of a fibrosis. With higher power, large masses of Gaucher cells are seen in the meshes of the interstitial tissue and also invading the peripheral portions of the lobules (Fig. 2). The large cells are also found in many of the sinusoids, but the stellate cells of Kupffer are not involved in the process. The individual hepatic cells are quite normal. A few masses of brownish pigment are seen here and there, especially in and near the walls of some of the larger bloodvessels. The thrombotic process in the

portal vein and its branches shows definite organization with the presence of many young fibroblasts. The fatal termination may be attributed, without question, to the extensive portal thrombosis.

In some of the livers that we have examined the recognition of the characteristic large cells is a matter of some difficulty, and it has been frequently necessary to employ special stains for their detection. In this case, however, the individual cells are quickly and easily detected by the usual staining methods, even in those places where a large number of the cells are compressed into extensive fused masses.

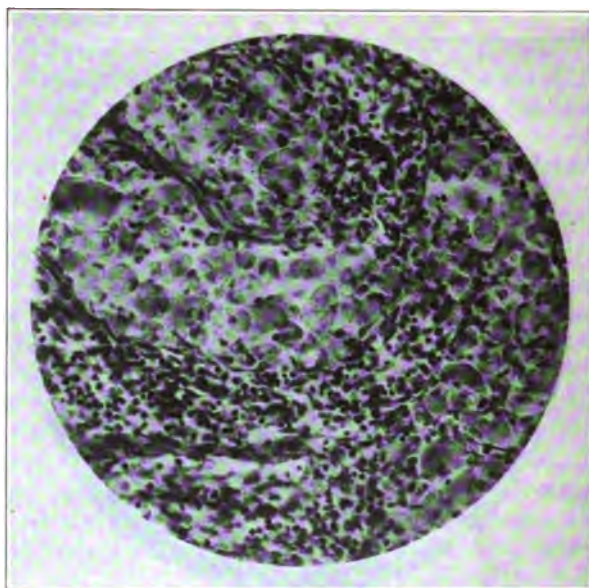


FIG. 3.—Section of retroperitoneal lymph node showing several alveolar spaces filled with large cells, also areas of normal pulp cells.  $\times 400$ .

**Lymph Nodes:** The degree of involvement varies in the different regional groups. The mesenteric and retroperitoneal nodes as well as the nodes at the hilus of the spleen and along the splenic vein show an advanced process, the nodes at the hilus of the liver a slighter degree of involvement, while the tracheobronchial and esophageal nodes present only an early stage. The nodes in which the process is far advanced show an almost complete disappearance of normal lymphadenoid structure, the entire node being replaced by the characteristic large cells (Fig. 3). Here and there in these nodes the remnants of a follicle may be seen, usually in the cortical zone. In one of the nodes at the hilus of the spleen, however, one portion was quite normal in appearance, while the remaining part showed a high degree of involvement, the cells here being fused

into long strands and large syncytial masses. In some of the retroperitoneal nodes the cells are of enormous size, and in one of these cells twenty-one nuclei were seen. The largest number hitherto recorded in a single cell is thirteen. In none of the nodes examined do the germinal centers show any abnormal activity, such as is frequently noted in cases occurring in infants or children. The quantity of pigment is variable, a large amount being seen in the esophageal and tracheobronchial nodes, in the nodes at the hilus of the spleen and along the splenic vein, and only a few granules in the mesenteric and retroperitoneal nodes. A positive iron reaction is obtained in some of the pigment only.

**Bone-marrow:** The large cells are seen singly and in extensive groups and present the general characteristics noted in the other hemopoietic organs. No pigment is seen.

**Other Organs:** A careful microscopic examination was made of the heart, aorta, lungs, thymus, kidneys, adrenals, pancreas and intestines. No large cells could be found in any of these organs, corroborating the findings in all previous authentic cases.

The lymph-adenoid tissue of the small intestine was found to be normal, but some pigmentation of the muscle fibers was seen. This observation has been made in other cases. The thoracic and abdominal aorta were carefully studied but no cellular changes were found.

The second case, therefore, is a typical instance of Gaucher's disease, conforming in its pathological aspects with eleven other cases which the author has had the opportunity of studying histologically.

**THE PRESENCE OF LARGE CELLS IN OTHER CONDITIONS.** Before proceeding to a description of the typical cells of Gaucher's disease a few remarks on other conditions accompanied by the presence of "large cells" may result in a clearer conception of the entire problem.<sup>6</sup>

It has been shown by numerous investigators that certain groups of cells, notably the reticular cells of the hemopoietic organs, are susceptible to the effects of various agents, bacterial, toxic, metabolic or chemical, the type of reaction depending in each case upon the nature of the irritant concerned. Thus, Mallory, in 1898, described certain cellular changes in the spleen, lymph nodes, bone-marrow and liver in cases of typhoid fever. He called the cells involved in this process "endothelial leukocytes" and recognized the biological importance of these cells reacting as a group to a definite toxin.

The tubercle bacillus is another agent capable of producing cellular

<sup>6</sup> The author may be pardoned in the following portion of the paper for referring rather extensively to the article on Gaucher's disease by Mandlebaum and Downey, inasmuch as no copies of the *Folia Hæmatologica* have been received in this country since the article was published,

reactions in this group of cells, especially in the spleen and lymph nodes. The cellular hyperplasia in the spleen in splenomegaly due to tuberculosis may be a prominent histological feature. In fact, two cases of this nature have been incorrectly classified in the literature as instances of Gaucher's disease, and the material from two additional cases, in which the diagnosis of Gaucher's disease had been suggested, has recently been submitted to the author for study. It should be mentioned here, however, that two typical cases of Gaucher's disease have been reported in which foci of tuberculosis have been noted (Schlagenhauser, Erdmann and Moorhead). These two cases conform in all respects to the other authentic cases unaccompanied by tuberculosis, and the tuberculosis here is evidently a superimposed process.

The injection of carmine or acid colloidal dyes into animals produces changes in the same specific group of cells, as shown by Kiyono and others, the cells having received different names by the various authors who have worked on the subject. These cells, the "histiocytes" of Kiyono and Aschoff, the "pyrrhol cells" of Goldman, the "resting wandering cells" of Tschaschin, the "macrophages" of Evans, are the fixed cells of the reticulum of the hemopoietic organs, the free cells derived from the reticulum, the Kupffer stellate cells of the liver, the clasmotocytes of loose connective tissue and the lymphoid cells of the milky patches of the omentum. The reaction of these cells in vitally stained animals has been fully described in the literature. This specific group of cells has been termed "endothelialer Stoffwechselapparat" by Landau and Aschoff.

The cells just mentioned are practically identical with the cells involved in storing lipoids in animals fed upon fatty substances or cholesterin, as shown by Anitschkow, and a striking resemblance to the lesions found in Gaucher's disease has been noted in these animals. The similarity is so marked, in fact, that Aschoff called the condition "pseudo-Gaucher." Anitschkow calls all the cells involved in this process "cholesterinesterphagocyten."

Experimental bacteremia, as shown by various authors, is often followed by marked activity of the reticular cells, as well as phagocytosis, the extent of the process and the type of cell involved depending upon the organism employed and the conditions of the experiment.

In 1912 Schultze called attention to important cellular changes in a case of diabetes associated with lipoidemia. In this case and in two cases of a similar nature subsequently published by Lutz the cellular reactions were limited to the spleen, but Lutz described areas of cholesterin cells in the aorta of his first case, recalling the lesion produced in the animal-feeding experiments of Anitschkow. In a case of the same type reported by Williams and Dresbach large cells were found in the liver and lymph nodes, in addition to the cellular hyperplasia in the spleen, and certain striking changes were seen in the adrenals suggesting those described by Anitschkow in

his animal experiments. Following Schultze's publication, in which he noted the resemblance to Gaucher's disease but erred in stating that the large cells of Gaucher's disease undoubtedly contain lipid substances, the subject has been somewhat confused and some authors have reported as instances of Gaucher's disease, other morbid processes accompanied by the presence of "large cells."

From what has been said above it is apparent that various factors may be concerned in the production of large cells; also, on purely biological grounds, that the histopathology and microchemical features of these cells must depend in each instance upon the etiological factor concerned. And it is also evident that all diseases or conditions in which large cells are found are not cases of Gaucher's disease. In cases of diabetes associated with lipoidemia, for instance, or in animals fed upon fatty substances, the large cells present histological and chemical characteristics never seen in Gaucher's disease or in the cells concerned in vital staining, one of the most striking features in the diabetic cases and in the animal experiments being the presence of anisotropic bodies and lipid substances in the large cells. These substances are never found in true cases of Gaucher's disease, as we have repeatedly shown.

An improper appreciation of the facts and observations just cited is one of the reasons for some of the errors in the diagnosis of Gaucher's disease and the limited number of detailed histological and biological studies of all of the above conditions is in part responsible for the controversies regarding the origin and nature of the reacting cells. The clinical factors and the histopathology of Gaucher's disease are characteristic and well-defined, and this disease should never be confused with other conditions. In our previous article we said that "the description of a single case may readily serve, with minor variations, as the basis for all the genuine cases reported," and this statement may with propriety be repeated again.

**THE LARGE CELLS OF GAUCHER'S DISEASE.** Following the first contribution to the subject in 1882 by Gaucher, considerable controversy has arisen in regard to the large cells, the chief discussion revolving about the question as to whether the cells are derived from endothelium or reticulum. The authors who have written upon the subject have been about equally divided on this point, and some have stated that the cells may originate from both sources. It is beyond the scope of this paper to present in detail all of the arguments brought forward by the various writers to prove their contentions, but the recent investigation of Mandlebaum and Downey seems to permit an accurate determination of the origin of the cells.

The large cells show considerable variation in size, the average diameter being from  $20\ \mu$  to  $40\ \mu$ , but occasionally cells of huge size are seen, three or four times as large as the average. They are round or oval in shape when more or less isolated, but when large compressed areas are found the cells are usually fused into long strands

or united as syncytial masses. The large cells show a strong affinity for acid stains which bring out clearly a network of fine fibrils running in a wavy, parallel course in the direction of the longitudinal axis of the cell. This gives to the cell its streaked or wrinkled appearance, but when the cell has been cut transversely to the main direction of the fibrils the cytoplasm appears granular or stippled. In many of the cells one sees irregularly shaped or elongated, colorless areas bounded by the fibrils which have been crowded apart. The shape of these colorless spaces is an important point of distinction between the Gaucher cells and the cells seen in the diabetic lipoidemia cases or in the animal-feeding experiments, for in the latter two conditions the colorless spaces or vacuoles are rounded. Furthermore, the characteristic streaked or wrinkled appearance of the Gaucher cells and their tendency toward fusion or the production of long bands are never seen in the lipoid cases; finally, multinuclear cells, common to Gaucher's disease, are never encountered in the diabetic lipoidemia cases. In addition to the cells just described, which are typical for the disease, other cells are seen with a more homogeneous cytoplasm and little or no evidence of fibrils or colorless spaces. As previously stated, the Gaucher cells never contain fat or lipoids, the microchemical and polariscopic tests for these substances being constantly negative. Glycogen, amyloid and oxydase are also absent and the cells remain unchanged after treatment with potassium hydrate or strong acids. Alcohol, ether, chloroform, acetone and xylol have no solvent action on the cytoplasm of the large cells, for there is no change in the staining qualities after the use of these reagents, excepting that the fibrillar structure is rendered more prominent and the cells appear somewhat shrunken.

The nuclei, as a rule, are irregular in shape, small in proportion to the size of the cell, and eccentrically placed. Many contain a considerable amount of chromatin and appear dark. Cells with two or more nuclei are common and as many as twenty-one were counted in a single cell in the second case just reported. The cells with homogeneous cytoplasm frequently contain nuclei which are larger than those just described, round or oval in shape, with one to three nucleoli. Other cells may show small, dark, pyknotic nuclei, apparently degenerating forms. Cell division by amitosis has been described by De Jong and Van Heukelom and by the writer.

The amount of pigment in the large cells is variable. As a rule it is more abundant in the large cells of the lymph nodes than in those of the spleen or liver. A large amount is usually found when extensive hemorrhagic areas are present. While most of the pigment is located in the fixed cells of the reticulum and in the reticular macrophages a certain amount may be found in the characteristic large cells. Some cells may contain so many pigment particles that the character of the cell cannot be determined. The pigment is bright yellow or brownish in color and may occur in the form of

crystals or as rounded, dense masses. When seen in the latter form it usually gives a positive reaction for iron. A certain number of phagocytic cells are seen containing erythrocytes, but it is impossible to say definitely whether these are true Gaucher cells. In a former paper the author stated that the large cells were phagocytic for erythrocytes, agreeing on this point with the claim made by Risel. In the subsequent studies made with Downey, however, this question could not be decided positively. A point in favor of the phagocytic character of the large cells is the intense blue color in some of the cells when the staining reaction for iron is made. This may be explained by a transformation in the cells of the hemoglobin products after phagocytosis into a soluble and diffusible iron compound.

Our observations on the histogenesis of the large cells were made chiefly in a study of the lymph nodes. These show different degrees of involvement in the various regional groups, and the process can be studied here with greater accuracy than in the spleen in which the lesion is usually so far advanced that the early changes may be more or less obscured.

In lymph nodes showing an early stage of involvement the reticulum, excepting that which forms the walls of the sinuses, is hypertrophied. In these nodes, as well as in the nodes with a more advanced process, the reticular cells of the sinus walls always remain normal and no large cells are seen within the lymph sinuses. The follicles are surrounded by a thick layer of cellular reticulum and the germinal centers contain large, phagocytic reticular cells. Isolated Gaucher cells are found here and there, and long bands of Gaucher tissue are seen directly continuous with the surrounding reticulum.

In the nodes in which the involvement is far advanced the follicles or remnants of follicles are always surrounded by a ring or wall of large cells and in the center of the follicles large cells are seen. The process begins in a small group of large cells in the germinal center or at the periphery of the follicle. These cells spread until the follicle is almost surrounded, and the cells also spread outward from the germinal center. In this way the follicle is gradually replaced by Gaucher cells and the lymphocytes gradually disappear. The significant fact, as shown by Downey, is that the Gaucher tissue occurs in those regions in which the reticulum shows distinct evidence of hypertrophy. The cellular reticulum in normal lymph nodes is very abundant in the germinal centers and a thick layer may surround the follicle. In both regions it changes its character very readily whenever the node is placed under abnormal conditions of any kind. Downey has shown by tracing strands of normal reticulum that they finally loosen up and assume the same identical structure as the Gaucher cells, proving beyond question that the Gaucher cell is merely modified cellular reticulum, that is, modified by the storage of some foreign substance taken up. This accounts for the apparent fusion of Gaucher cells into syncytial masses and

for the long cells, and also for a reduction in the amount of normal reticulum within the masses of Gaucher cells (Fig. 4). It must be noted that the disappearance of normal reticulum applies to its cells, for the fibers may be present in normal numbers, forming a close network around the Gaucher cells. Most of the reticular fibers are merely in contact with the surface of the cells, but some cells are found which contain fibers within their cytoplasm, as noted by Downey. This is also strong evidence that the Gaucher cells are modified reticular cells. During the progress of the disease most of the cells become detached from the fibers and become isolated cells. This often occurs in normal nodes and the reticular cells

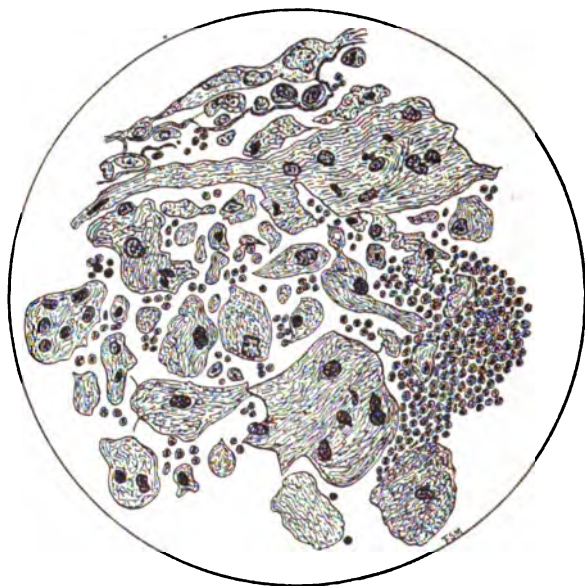


FIG. 4.—Section of lymph node at hilus of spleen. Near the upper border is a strand of normal reticulum which spreads out, assuming the structure of the cytoplasm of the large cells. The character of the Gaucher tissue is seen in the syncytial masses. A sinus wall with normal "endothelium" is seen at the upper border. Camera lucida drawing, Zeiss apochrom. obj. 4 mm., ocular 6.

become free wandering cells. The reticular fibers may also disappear, probably owing to the fact that they have become separated from their cells.

The so-called "endothelium" which lines the sinuses is absolutely normal. The present view is that this "endothelium" is really part of the general reticulum. The cells here in normal nodes are very active as phagocytes, often separate from their fibers and enter the sinuses as free cells (endothelial leukocytes of Mallory). Some reaction might be expected in Gaucher's disease in this reticulum, but our study shows that this reticulum is always normal no matter how advanced the process. The Gaucher cells, therefore, are



certainly not of "endothelial" origin, and our material shows no evidence for the transformation of the reticulum bordering any of the sinuses of the lymph nodes into Gaucher tissue.

It is difficult to say why the reticulum of the sinuses should show no reaction in Gaucher's disease, but other analogous conditions are also difficult to explain. In the Anitschkow animals the feeding of cholesterin caused the appearance of lipoid-containing cells in the intima of the aorta, but the endothelium was unaffected. Similarly, in vital staining the reticulum forming the sinus wall is very active and reticular cells in other parts of the node show great avidity for the dye particles, while those in the germinal centers take up little or none of the dye. In Gaucher's disease most of the reticulum may become transformed into the characteristic tissue, but many normal reticular cells not affected by the process may be found. Mechanical conditions may possibly play an important part and the free circulation of lymph through the sinuses may be a factor in keeping the cells normal in Gaucher's disease, while in the vitally stained animals the dye is brought into the node through the lymph vessels and comes into direct contact with the reticulum of the sinuses. If the substance in the cases of Gaucher's disease is brought to them through the lymph stream one would expect the reticulum of the sinuses to react as it does in the dye animals and assume the character of Gaucher tissue. The fact that it does not react in this way is an argument in favor of the view that the substance is produced by the reticular cells and stored within their cytoplasm. On the other hand, one must not overlook the fact that in Anitschkow's animals the lipoids passed between or through the endothelial cells of the aorta and were stored in the cells of the intima, leaving the endothelial cells unchanged. One must also remember that the endothelium of blood and lymph vessels does not show the same avidity in taking up foreign substances as does the reticulum of the lymph sinuses. One cannot draw definite conclusions in regard to the origin of the substance in the Gaucher cells from these examples, for the reactions in experimental lipoidemia and in vitally stained animals are not exactly parallel. A comparison of the reactions of the reticulum in Gaucher's disease with the reactions in vitally stained animals is against the exogenous origin of the substance, while comparison with the lipoidemia cases is, to some extent, in favor of such an origin. Viewing the question from a biological standpoint and also taking into consideration the fact that the cellular reticulum of the hemopoietic system is not a highly specialized tissue, the writer is inclined to the opinion that the substance contained in the large cells is exogenous rather than endogenous in origin.

Downey has noted that the connective-tissue cells of the liver and of the walls of its veins may become transformed into Gaucher cells identical in structure with those of the lymph nodes and spleen. The reticulum lining the sinusoids (Kupffer cells) is not involved in

the process, therefore the origin of the free Gaucher cells within the sinusoids must be accounted for in some other way. That these cells are carried into the liver through the splenic vein seems probable, as the Gaucher cells are frequently seen in the larger branches of the portal vein. There is no evidence for an endothelial origin of the cells in the liver and no evidence that the cells proliferate in the liver after being carried through the splenic vein. It remains uncertain whether the Gaucher tissue of the liver represents modified fibroblasts or reticular cells. According to Rössle and Yoshida, who have described the transformation of reticular tissue to collagenous tissue, it may be assumed that the same cells may produce both reticulum and collagenous fibers and that there may be no fundamental difference between fibroblasts and reticular cells. The parent cell may, therefore, produce a reticular cell, a fibroblast or a Gaucher cell.

From what has been described in the lymph nodes, it is evident that the histogenesis of the large cells in the spleen is the same, but the process in the spleen in all the cases we have examined is too far advanced to permit of the same accurate determination as in the lymph nodes. On account of the direct communication of the sinuses with the surrounding pulp, it seems possible that most of the free Gaucher cells within the sinuses have come from the surrounding pulp and are derived from the reticulum. There is no positive evidence in the spleen, however, that the endothelium of the sinuses does not take part in the formation of the large cells, and the possibility of derivation from this source cannot be denied. The fact that the walls of the dilated sinuses containing Gaucher cells are composed of a dense fibrous tissue, usually without an endothelial lining, is in favor of this view. In the bone-marrow it may be assumed that the Gaucher cells are derived from the reticulum, inasmuch as the marrow contains a reticular framework similar to that of the lymph nodes.

From the foregoing description it may be seen that a definite and characteristic reaction of the reticulum of the hemopoietic system occurs in cases of Gaucher's disease. Although the changes in some of the organs bear a certain resemblance to other conditions, such as the diabetic lipoidemia cases and the reactions in cholesterol-fed animals, a clear distinction may be made histologically and chemically in the character of the large cells, and the claim of practical identity of Gaucher's disease with lipoidemia cases is not justified.<sup>7</sup>

**STUDIES OF LIPOIDS.** The subject of lipid substances in the large cells of Gaucher's disease has now been investigated in 6 cases, 4 children and 2 adults. In 2 of the cases it was possible to use only material fixed in formalin, but in the remaining 4 cases (2 children, 2 adults) fresh material was also employed. In all of these

<sup>7</sup> A critical study of the histopathology of vitally stained animals, diabetic lipoidemia cases and cholesterol-fed animals as compared with Gaucher's disease is given in the paper by Downey and the writer.

cases the observations were made chiefly upon frozen sections of spleen. In 1 case, however (Case II, reported above), studies were also made of the fresh liver and bone-marrow. The chemical and polariscopic tests were uniform in all of the cases, therefore it is unnecessary to specify each case individually.

Frozen sections of fresh spleen stained with Nile blue, Sudan III and Scharlach R are always negative (absence of neutral fat, cholesterin esters, lipid substances, fatty acids and soaps). Nile blue often shows a faint bluish color of the entire section, but the normal pulp cells hold the stain more than the large cells. The Smith-Dietrich method produces either a very light grayish-blue color or a dirty brown color of the large cells, depending upon the duration of the stain and the amount of differentiation, but no lipid or myelin substances can be detected. Fischler's method shows a light, diffuse, bluish color in some of the cells, while other adjoining cells remain colorless. No blue-black granules or crystals (glycerin esters, fatty acids or soaps) are found in any of the large cells. Ciaccio's methods show a few isolated spherical bodies of minute size, yellowish orange in color, in some of the cells. These are not more numerous than one might expect in any tissue treated by this method.

Weigert's myelin sheath stain, which, according to Schultze, gave a positive reaction in his case of diabetes, is entirely negative. The large cells show a pale, grayish color, homogeneous in character, but no lipid substance is seen. These sections were stained with iron-hematoxylin for twenty-four hours, and after differentiation were cleared in benzin as well as in xylol. The Weigert-Van Gieson method as recommended by Schultze is also negative. Some of the latter sections were overstained, decolorized by acid alcohol and cleared in benzin, but the results were constantly negative. Sections treated with osmic acid for twenty-four hours and then exposed to the light for the same length of time are negative. Sections stained with neutral red are also negative, the entire section being faintly red, the large cells holding the color least of all. Sections tested for cholesterin, fats and free fatty acids by the Golodetz method and by Lugol's solution followed by sulphuric acid, 30 per cent., are also negative. With the latter test a brown color appeared, but no change into blue or green after an observation of thirty minutes. Crystals of cholesterin as control for these two methods showed positive reactions in both instances.

Unstained frozen sections examined with the polariscope show no double refracting substances (cholesterin esters, myelin substances). All of the sections stained with Nile blue were also examined with the polariscope, but anisotropic bodies were never seen.

The liver of Case II was examined in the fresh state. Polariscopic examination of frozen unstained sections as well as sections stained with Nile blue are negative for double refracting substances. Sudan III shows a few red droplets in the liver cells here and there (fatty

degeneration), but no reaction in the large cells. Smears made from the fresh bone-marrow in the same case show no anisotropic bodies by polariscopic examination.

Assuming that lipoids might be present combined in a highly complex protein molecule and hence difficult to identify microchemically, an attempt was made to break up this combination by the action of artificial digestive fluids. Thin blocks of formalin-fixed spleen were treated with ammonium hydrate, 2 per cent., for one hour, to neutralize the formalin and then washed in running water for eighteen hours. Frozen sections were made and placed in a solution of pepsin, 0.1 per cent., hydrochloric acid, 0.2 per cent., in an oven at 37° C. Sections were then stained with Nile blue and Sudan III and also examined with the polariscope at intervals up to 100 hours, but no reactions for fat or lipoids could be obtained. The activity of the fluid was evidenced by a slow digestion of the tissue after sixty hours, but a sufficiently large number of the Gaucher cells remained for the tests. Other sections were subjected to the action of trypsin, 0.5 per cent., and sodium bicarbonate, 0.5 per cent., and stained as above at intervals up to fifty hours. The reaction for fat or lipoids was also negative in this series. In both instances the staining qualities of the large cells remained unchanged, showing no fission of the combination in the cells.

A complete chemical analysis was made in 3 cases in order to determine the presence of fats or lipoids, for it was recognized that these substances might be present despite the negative results of microchemical tests. The material employed for this work consisted of 5 grams of spleen fixed in formalin from each of 2 cases occurring in children (Case I and Case II in table) and 100 grams of fresh spleen and an equal amount of formalin-fixed spleen from the male adult case reported in this paper (Case III in Table).<sup>3</sup>

*Technic.* The material was first dried on a water-bath and for two successive days for three hours each, in a drying oven at 70° C., until a constant weight was reached. The material was then extracted in four times its volume of absolute alcohol at 37° C. It was then filtered and the entire process repeated three times. Extraction in a Soxhlet apparatus with absolute alcohol for ninety-six hours followed. This process was repeated with ether and chloroform each for ninety-six hours. The entire extractives were then mixed, evaporated to a small volume and transferred to a large weighed platinum dish. The material was then evaporated to dryness in the air, placed in a drying oven at 70° C. for three hours and weighed. It was then redissolved in hot absolute alcohol and immediately filtered to eliminate any salts. It was then re-evaporated, re-dried and re-weighed. The process was repeated until a constant weight

<sup>3</sup> It is a great pleasure to thank Dr. M. A. Rothschild for the chemical examination of the two children's spleens and for valuable coöperation throughout the lipid studies, and Dr. S. Bookman for his kindness in performing the analysis of the adult case and for his keen interest in the entire chemical investigation.

was obtained, thus obtaining the total weight of the extractives. It was then redissolved in 250 c.c., of mixed solvents, ether, absolute alcohol and chloroform. It was then divided into five portions of 50 c.c. each. Two 50 c.c. portions were used for nitrogen determination, employing the Kjeldahl apparatus; 50 c.c. were used for the phosphorus determination, the phosphorus being determined as  $Mg_2P_2O_7$ ; a fourth portion was used for total cholesterol determination, employing the Autenrieth-Funk colorimetric method.

The fatty acids were determined by shaking 50 c.c. of the mixed solvents with sodium hydrate, 10 per cent., in a separating funnel. The watery solution containing the free fatty acids was separated from the mixed solvents, acidified with phosphoric acid and shaken out with ether. It was purified until a constant weight was reached and its acidity determined in terms of stearic acid, using a  $\frac{1}{10}$  normal solution of sodium alcoholate and phenolphthalein as an indicator.

The mixture of combined or saturated fatty acids which had been separated from the watery solution was saponified with alcoholic sodium hydrate on an electric bath with a return condenser for six hours. The solution was evaporated until no trace of solvents was present, acidified with an excess of phosphoric acid and extracted with ether. The fatty acids were determined as above and the acidity ascertained in terms of stearic acid.

LIPOID CONTENT OF SPLEENS. TABLE I.

	Case I.	Case II.	Case III.	
	Dried formalinized spleen.			Dried fresh spleen.
	Per cent.	Per cent.	Per cent.	Per cent.
Extractives . . . . .	34.4	23.47	19.895	27.687
Cholesterin . . . . .	1.86	1.77	10.151	9.214
Lecithin . . . . .	14.29	17.2	3.71	3.448
Nitrogen . . . . .	0.59	0.66	0.503	1.539
Free fatty acids . . . . .	2.7	1.5	2.804	0.000
Combined fatty acids . . . . .	9.9	2.7	5.835	19.948

The following figures are obtained from Table I, calculated as percentages of the extractives:

TABLE II.

	Case I.	Case II.	Case III.	
	Dried formalinized spleen.			Dried fresh spleen.
	Per cent.	Per cent.	Per cent.	Per cent.
Extractives . . . . .	34.4	23.47	19.895	27.687
	Percentage of extractives.			
Cholesterin . . . . .	5.4	7.50	51.018	33.282
Lecithin . . . . .	41.4	73.40	17.442	12.454
Nitrogen . . . . .	1.8	2.81	2.527	5.558
Free fatty acids . . . . .	8.0	6.40	14.101	0.000
Combined fatty acids . . . . .	28.6	11.70	29.344	72.048

*Discussion of Chemical Findings.* At the present status of our knowledge of the chemistry of organs we do not feel warranted in drawing any very definite conclusions from the analysis of three spleens. It is interesting, however, to point attention to the similarity of the chemical findings in Cases I and II and the variation in Case III. The cholesterin-lecithin fraction of the extractives in all three cases varies from 46 to 80 per cent. There is no great variation in the total amount of cholesterin in the first two cases; in the third case, however, the cholesterin figure is much higher. This again illustrates the well-known fact that microchemical examination is no index of quantitative chemical determinations. Despite the seemingly large amount of cholesterin in Case III the microchemical tests here, as well as in Cases I and II, gave absolutely no indication of its presence.

We are presenting these figures as a matter of record, with the hope that chemical analyses of normal and pathological spleens in the future may throw more light on this obscure condition. A critical study of the findings, however, may warrant the assumption that the peculiar substance in the cells, which is so characteristic of Gaucher's disease and which has never reacted to any microchemical method for lipoids, is not of pure lipid nature. The substance does not lie in the extractive group, but is, in all probability, of complex protein nature in combination with lipoids.

**CONCLUSIONS.** Gaucher's disease is characterized by a distinctive, well-defined clinical picture and constant, definite changes in the hemopoietic organs. The presence in these organs of peculiar large cells with a characteristic type of cytoplasm, not duplicated in any other disease, is a distinguishing histological feature. These cells are derived from the reticular apparatus of the hemopoietic structures, but an additional origin from the endothelial cells of the venous sinuses of the spleen cannot be denied. Fat or lipid bodies cannot be found in the large cells by microchemical or polariscopic tests. The peculiar substance in the large cells does not lie in the extractive group, on chemical analysis, but is apparently of complex protein nature in combination with lipoids. The disease is evidently caused by some disturbance of metabolism, the products being found in a specific group of cells (reticulo-endothelial) of the hemopoietic system.

Other diseases as well as some lesions produced experimentally in animals may be accompanied by the presence of large cells involving the same specific group of cells that are concerned in Gaucher's disease. This group, as has been shown, may react in various ways to many forms of irritation, chemical, bacterial, metabolic or toxic in character, but the changes in each instance are dependent upon variable etiological factors, and a clear distinction between these cellular reactions and the large cells of Gaucher's disease may be made microchemically and histologically.

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**STANDARDIZATION OF METHODS IN CASES OF PROSTATIC OBSTRUCTION.**

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THAT marked benefits follow the standardization of methods in medical therapeutics is a fact sufficiently patent today to need no detailed emphasis. While the setting up of established rules is of value in any branch of science, it is especially in those branches dealing with the actual treatment of disease entities that the most direct and gratifying results are obtained. In no instance is this seen more clearly than in the history of surgical procedures of all kinds. Consider, for instance, a single illustration: the surgery of hernia. In his article in Keen's surgery, Coley states that in 1890 the most reliable statistics of the results of operation showed from 30 per cent. to 40 per cent. relapses within the first year; and an immediate operative mortality of about 6 per cent. Today the operation is followed by permanent cure in about 95 per cent. of all cases and the operative mortality has fallen to one-quarter or one-half per cent. These marked improvements have been due in greatest measure to standardization of method (Bassini), and to a clearer and more widely diffused knowledge among surgeons of the principles underlying operative treatment. Similar improvement can be demonstrated to have followed our dealings with the appendix; the cancerous breast or uterus; the stomach, gall-bladder and intestines.

Before becoming well established and of universal application almost all surgical operations have gone through four stages. The first is when the operation is performed by a few pioneers, often men ahead of their generation in ability and imagination; always clear thinking, hard struggling. Later there comes a more universal adoption, as the knowledge of the benefits to be hoped for becomes diffused, till a third stage is reached when the operation though widely attempted is sometimes handicapped by modifications of many sorts; often unnecessary, frequently harmful. With the passage of time, however, the unnecessary is dropped, the essential retained and a few basic rules established; in short, the operation becomes standardized and the real permanent benefit in the immediate mortality and remote results is seen.

The treatment of cases of prostatic obstruction is at present just entering this final stage. Even today one may find the mortality following operation as high as 15 or 20 per cent. in some instances, whereas in the hands of many others this has been reduced to from 6 to 3 per cent. or even less. Efforts to standardize the treatment



and operation are constantly being made, but it is evident that more still are necessary.

The surgical problem of the patient afflicted with prostatism is peculiar in that he is usually at an age of declining vigor. It is very exceptional to find such a patient whose heart and kidneys are still normal. Standardization of the methods of preoperative treatment therefore is of the first and utmost importance. Besides the local condition at the bladder outlet the general condition of the patient in each instance demands careful attention.

The general examination should consider in all cases the normality, or degree of departure from this, of the circulatory system. The blood-pressure, both systolic and diastolic, should be measured and charted. If there is any very evident abnormality of the heart action an analysis of this by the electrocardiograph often gives a clear index for treatment before venturing on operation. The fact that many of these patients are tending toward uremia should never be forgotten, and special watch should be kept for signs of acidosis. Headache, occasional slight mental confusion, dry mouth and tongue and buccal dysphagia are the earliest signs which in my experience point to impending uremia. Occasionally mild grades of the dyspnea of acidosis are seen.

Of even more importance than the condition of the heart is that of the kidneys, so that the renal function should be considered most carefully. An estimation of the ability of the kidneys to excrete foreign dyes is judged by the injection of phenolsulphonephthalein, while the degree of retention of waste products is found by measuring the urea nitrogen of the circulating blood. These two tests form the basis of all successful preoperative care of prostatic patients and should be carried out frequently. Of special importance in the examination of the urine is its quantity, which should be noted each day together with the specific gravity. An output greater at night than during the day, and of a persistently low gravity, is significant of serious renal damage. Note should also be made of the degree of infection of the bladder and kidneys as estimated by the amount of pus which the urine contains. As is well known, the prostatic with uninfected urinary system is often a poorer operative risk than the patient who being infected has established a resistance thereto. That the infected patient is a better risk is only relatively true, however, for it is often with signs of entire failure of renal function from overwhelming pyelonephritis that such cases die. There is, therefore in every case a clear indication for doing whatever is possible to prevent infection and to help the patient to fight it when it exists.

An adequate knowledge of the local conditions at the neck of the bladder is imperative. By rectal touch one determines the size of the prostate, its consistency, its degree of tenderness, as well as whether or not it is adherent and whether or not the notch is preserved. By catheter the amount of retained urine is noted and by

cystoscope the exact configuration of the obstructing masses as well as the presence or absence of bladder stone, diverticulum or tumor are learned. I am strongly of the opinion that with a very few special exceptions no surgeon is justified in undertaking the operative removal of a prostate which he has not previously examined *personally*, both by rectal touch and by cystoscope. He certainly will not so operate if he desires the lowest possible mortality rate. It is well to remember that cases of obstruction to urination occur frequently in which no enlargement of the prostate by rectal touch can be found. In these instances the difficulty is caused by a median bar or middle-lobe hypertrophy, conditions which can only be determined by the cystoscope. In such cases palpation of the prostate by rectum while the cystoscope still fills the urethra is enlightening.

A clear recognition of the great importance of the factor of urinary retention in causing back pressure on the kidneys, and thus seriously interfering with their functional power, has been the most notable contribution during the last decade to the subject of prostatism. Therefore the surgeon's first and most pressing duty is to relieve the retention and put the bladder at rest. There are two methods by which this can be accomplished: either by the use of the constant inlying catheter or by an artificial opening made in the bladder above the pubes. Each method is equally efficient, and according as the other factors enter, such as the type of prostatic enlargement and the kind of operative attack proposed, will the choice of one or the other be made.

With the above considerations in mind the preoperative care of the prostatic will be seen to be well standardized by the following rules used at present in the Peter Bent Brigham Hospital.

**PREOPERATIVE TREATMENT AND MANAGEMENT OF CASES OF PROSTATIC OBSTRUCTION.** *Forcing Fluid.* Each case of prostatic obstruction is to be given water by mouth as follows: every hour during the day 180 to 200 c.c. The same amount every three hours at night. If the patient cannot take approximately this amount of water the difference should be made up by rectal injection or hypodermoclysis. Cardiac complications are a contra-indication to this procedure. Record the fluid intake and output on the chart.

*Urinary Antiseptics.* In all cases give hexamethylenamin, grams 1.0 t. i. d., after demonstrating the fact that urine is acid. If this is not the case give sodium benzoate, 0.5 gram t. i. d., until acidity is established, then give hexamethylenamin.

*Urine Analysis.* Every other day, or oftener if the condition necessitates, an analysis of the urine is to be made from the twenty-four-hour specimen and recorded. This includes the microscopic examination of sediment as well as the estimation of its amount.

*Diet and Bowels.* The diet should be liberal. House diet is sufficient as a rule. Special attention should be paid to keeping the bowels active, so that at least one dejection is obtained each day.

*Blood-pressure.* Blood-pressure readings should be made on the entrance of the patient and at least every three or four days thereafter.

*Relief of Urinary Obstruction.* All cases showing residual urine on entrance should have the bladder put at rest by one of three means: (1) inlying catheter; (2) intermittent catheterization; (3) suprapubic cystotomy.

Every catheterization should be done under rigid aseptic precautions. The operator's hands should be washed with soap and water, alcohol or corrosive. The penis should be washed with soap and water and corrosive. Sterile forceps are better than the hand for inserting all catheters except those bearing a stylet. The safest lubricant is glycerin, recently sterilized.

*Inlying Catheter Routine.* If possible this should be a soft-rubber instrument, size 24 to 26 F., passed on a wire stylet. It should be attached in place by adhesive strapping. Wash the bladder through the catheter each morning and night, using 1 liter of warm 1 to 60,000 bichloride of mercury or 1 to 5000 silver nitrate. Do not distend the bladder over 200 c.c. at a time. Failure of the catheter to drain at any time should be immediately reported by the nurse to the surgeon in charge of the ward. Remove the catheter every three days and wash out the urethra from the meatus with 1 to 5000 silver nitrate. Reinsert the catheter (reboiled or a new one) in from four to six hours.

Except when there is some contraindication, such as cardiac decompensation, the patient should be urged to be up and about the ward in a chair or walking a little each day. Under these conditions the catheter can be corked. It must be opened every four hours to empty the bladder.

Watch for any evidence of infection, such as severe urethritis (tenderness of urethra as palpated over catheter) or epididymitis, and in such cases remove the catheter and wash out the bladder and urethra with 1 to 5000 silver nitrate. Then employ:

*Intermittent catheterization*, passing the instrument every six hours during the day and once during the night. Inject into the bladder 50 c.c. of 1 to 10,000 silver nitrate after each operation and allow it to remain there.

*Suprapubic cystotomy* should be reserved for those cases in which, because of infection, severe pain or bleeding, catheterization cannot be instituted.

*The Phenolsulphonephthalein Test.* This should be carried out on each case on admission and every fourth day thereafter until operation.

Empty the bladder by the catheter. Inject intramuscularly 6 mg. (1 c.c.) of dye and note the time of the injection. Collect the urine coming from the catheter immediately after the injection into a flask with 2 to 3 c.c. of 10 per cent. sodium hydroxide and note the

*appearance time* of the dye. One hour later collect the urine and again at the end of the second hour. Estimate the percentage of dye in each collection separately. This should be done by daylight or white artificial light, and within a short time after the last collection is made.

*Blood Urea Nitrogen.* Ten cubic centimeters of blood are to be collected from an arm vein under aseptic conditions and sent to the laboratory technician for estimation and report.

The three groups of phenomena in these cases to be watched for and guarded against are those of (1) increase of infection of any part of the urinary passages, (2) uremia, (3) cardiac decompensation.

Careful observation of the patient's condition under such a régime as this will determine the time when the operation may safely be undertaken. It is important not to be deceived by a phthalein reading well within the normal limits (even 40 to 50 per cent.) when the patient is first seen, especially if he has a large amount of residual urine. Such readings are often seen to fall sharply during the first days of bladder drainage. But as the relief of back pressure on the kidneys continues, their function becomes slowly better, so that when the output of the dye has reached a stable figure, an operation may safely be attempted which would have been most hazardous earlier.

The time devoted to preparation of the patient for operation is thus seen to be a very variable one. In our experience it has averaged about a week or ten days; but this may be reduced to three or four days in some cases, while in others a month or more of pre-operative care is necessary.

Two ways of reaching the prostate exist—through the perineum and transvesically—and while it is not our purpose to describe these operations in detail here, it will be necessary to give a brief outline of each, especially as regards its applicability under differing conditions:

**THE PERINEAL OPERATION.** The earliest operations for removal of the prostate followed the perineal approach, and although many difficulties were experienced by the pioneer operators, this approach as modified by several surgeons, especially Young, is still of great value and should be the method of choice in many instances.

The two outstanding advantages of the perineal operation as compared with the suprapubic lie in the control of hemorrhage and in the easy and short convalescence. The gland having been removed there is left a cavity *external* to the bladder itself which can be nicely and accurately packed with gauze in a manner quite impossible when the approach has been transvesical. Also, for reasons not always quite clear, this form of operation is well known from clinical experience to cause less immediate prostration to the patient. Each of these points plays a part in promoting a quick, relatively comfortable convalescence.

A still further and very important advantage of the perineal operation is in regard to the question of malignancy. The incidence of prostatic cancer is unfortunately quite high, some clinics finding it in as much as 20 per cent. of their cases. This is probably a greater proportion than that seen, as a rule. In our own experience about one of each eight or ten cases is found to be malignant. The malignancy *always* begins in the posterior lobe, that portion of the gland which is first seen and examined by the perineal operation, but not seen at all by the transvesical approach. In any case, therefore, where the least suspicion of malignancy has been raised by the clinical examination, operative investigation of the gland from its perineal aspect is imperative.

The most marked disadvantage of the perineal approach lies in the fact that it is a relatively difficult operation in the hands of those who have not given special attention to perfecting themselves in it in all its details. The anatomical proximity of the prostate to the rectum has sometimes led to wounds of this structure and subsequent fistula. In other instances opening the urethra at a point too far below the tip of the prostate, and thus cutting the external or voluntary sphincter, has led to incontinence, partial or complete. Furthermore, unless the operator has been able to make a careful cystoscopic survey of the prostate before operation, he may by the perineal route overlook an hypertrophied middle lobe and find his patient after the operation still unable to empty the bladder with success in spite of the fact that "the prostate has been removed." I have personally seen instances of each of these difficulties.

For these reasons, especially, the perineal operation has failed to gain in popularity in the eyes of many surgeons. That this lack of popularity is undeserved I am sure anyone will quickly admit should he have the opportunity to follow to the end-result a series of cases of prostatectomy performed by this route and to compare this with a like series done by the suprapubic method. The situation may fairly be summed up by the statement that the perineal operation is harder on the surgeon than the suprapubic, but is easier on the patient.

To overcome the difficulties of the perineal operation three things are necessary: (1) the surgeon himself must be able to use the cystoscope and to *understand what he sees*; (2) he must know the anatomy of the perineum accurately, both in the cadaver and in the living patient; (3) he must have the operating room facilities for placing his patient in the high lithotomy position, which can only be secured by the use of a board such as that devised by Professor Halsted, since no operating table yet on the market will give sufficient elevation. The exaggerated position is absolutely essential, since it puts the perineal structures on the stretch and makes it possible to do the whole operation under the guidance of the eye. Only too often have I seen a surgeon vaguely operating in the depths of a

perineal wound, unable to see, uncomfortable and uncertain of just what structures, or portions thereof, were being removed; and all the difficulty due to the fact that he had his patient in the low lithotomy position, such as is used for a curettage of the uterus or the removal of hemorrhoids.

A brief summary of the steps of the removal of the prostate by the perineal route is as follows: The patient should be placed in an exaggerated lithotomy position; the incision should be made with anterior curve connecting each ischial tuberosity with the bulb of the urethra; exposure of the membranous urethra and introduction of tractor through a longitudinal incision in same; exposure of posterior surface of the gland and palpation for areas of possible malignancy. Vertical incisions into prostate on either side of the midline, through which lateral lobes are enucleated. Removal of tractor and insertion of index finger to palpate the region of the median lobe. If this be found enlarged, it should be enucleated. Insertion of a No. 30 F. soft-rubber catheter into the bladder and packing of each lateral cavity about this tube with gauze tape impregnated with kephalin. Union of the levator ani muscles in front of the rectum with one catgut stitch and closure of the wound. On being placed in bed the patient is immediately given 750 c.c. of saline solution by hypodermoclysis.

**THE SUPRAPUBIC OPERATION.** The transvesical approach to the prostate has many warm advocates, and when used in properly chosen cases, removal of the gland by this route is an eminently satisfactory operation. Since it can easily be performed in two stages, it permits easy and safe drainage of the bladder and consequent relief to the kidneys by a simple cystotomy above the pubes under local anesthesia. Later, the condition of the patient having improved, the prostate can be enucleated in a short operation performed under free view and with accurate appreciation of the obstructing mass by bimanual palpation.

In any considerable number of patients suffering from prostatism in whom it is imperative that the bladder be put at rest and the kidneys relieved, there will be found not infrequently cases that cannot tolerate an inlying urethral catheter. The reason for this is usually found in an acute infection of the prostate and prostatic urethra coexisting with the enlargement. In the hands of a skilful, especially trained orderly or nurse such cases can be tidied over the acute discomfort to a stage in which the catheter is satisfactorily tolerated. But such assistants, experienced in all the numerous minor adjustments necessary in difficult cases, are not always at the command of even the best-equipped hospitals. The efforts of the average house surgeon are rarely of avail. Repeated ill-advised manipulations with frequent prodding by catheters of varying sorts only increase the discomfort of the patient, which is already great, and make for increase of infection

and irritability of the already swollen prostate. Under such circumstances the bladder should be opened above the pubes forthwith.

The suprapubic operation will also strongly appeal to those surgeons who are unfamiliar with the use of the cystoscope as a means of preoperative diagnosis. With the bladder open they can see definitely that with which they must deal. Another group of surgeons, entirely unfamiliar with the proper type of perineal operation, will naturally choose the easier operation.

But leaving such instances aside, and omitting from consideration prostatic malignancy, let us ask the nature of the disadvantages of the suprapubic operation. To my mind there are two: a major one and a minor one.

The first of these concerns the control of hemorrhage after enucleation has been performed. One has but to review the several devices and methods still employed to appreciate quickly that there is no one of them in general favor. One surgeon uses pressure by the Hagner bag or a modification of this; another packs the cavity with gauze for a longer or shorter time; still others employ sutures or ligatures. The truth is that the mechanical situation which leaves a cavity containing torn vessels, often of considerable size, uncontrolled at the most dependent portion of the bladder, which must inevitably contain urine and often bacteria, and which must be drained against gravity, is inconsistent with the laws of sound surgical practice. The danger of postoperative hemorrhage is therefore an ever-present one, for the prevention of which measures should always be carefully taken.

The second disadvantage of the suprapubic operation concerns, as a rule, only those cases which have had the so-called two-stage operation, and is that of imperfect and slow healing of the twice-opened wound through the abdominal wall and bladder. After the abdominal muscles and bladder wall have tolerated the presence of a constant drain for ten days or more there is often found a lack of plasticity resulting from the infiltration of the tissues by an inflammatory reaction sometimes of considerable extent. This not only makes a second entrance into the bladder at this time more difficult than at the first operation, occasionally carrying the risk of inadvertently opening the peritoneal cavity, but it also prevents speedy and firm closure of the structures involved. Thus the convalescence after a two-stage suprapubic prostatectomy is frequently tedious and annoying for the patient. The constant presence of dressings saturated with urine, unless some special means be employed to avoid this, is also often extremely distasteful to patients of a certain type.

It is clear that if the methods of preventing postoperative hemorrhage can be standardized, this most prominent objection to suprapubic prostatectomy will be controlled. Although, as mentioned already, the measures advocated for this purpose are numerous, I

am sure that only when such measures include the basic surgical principles of exact ligature or suture of definite bleeding-points will they prove continuously of avail, and therefore become standard. I wish strongly to advocate, therefore, a suprapubic opening of the bladder throughout almost the entire extent of its anterior aspect, thus making possible adequate retraction and easy access to the region of the neck of the bladder after the prostate has been removed. Following this removal the cavity is best temporarily packed with gauze or tape impregnated with some styptic, such as kephalin. This is left in position for a few moments, and after its removal all those bleeding points which remain are controlled by accurate ligatures of plain catgut passed on a curved needle. Naturally such a procedure adds a few minutes to the duration of the operation, but there is no doubt that the safety of the patient and peace of mind of the surgeon thus secured, are well worth the extra time.

It is thus seen that the practices of the "five-minute prostatectomist" are to be entirely condemned. No doubt anyone foolish enough to attempt it can hastily insert one or two fingers into the bladder through the opening made at an earlier operation, tear out the prostate, adjust a large tube in the abdominal wall and get the patient off the operating table all in five minutes. It is possible to do this, but no patient is a fit subject for such a major operation as that of prostatectomy if his condition is so poor that it will permit of but five minutes of general anesthesia. The grave dangers of such haphazard operating are self-evident, and have done much in the past to keep high the mortality of this special operation. Fortunately operators so little cognizant of the principles of good surgery are not common today.

In regard to the second and less important difficulty which concerns slow healing of the suprapubic wound, we must accept this as in a measure inevitable. Careful mobilization of the anterior wall of the bladder from the under surface of the recti, mobilization also of these muscle bellies behind their sheath, followed by accurate approximation and suture, will do much toward promoting an early closure. If facilities are at hand for the proper care of such suction apparatus as that of Bethune, its use will go far toward the comfort of the patient by keeping the dressings almost, if not quite dry. An outline of a standard two-stage prostatectomy is as follows:

**FIRST OPERATION.** *Suprapubic Cystotomy.* Local anesthesia with one-half of 1 per cent. novocain. Patient in slight Trendelenburg position. Infiltration of the skin in the middle line above the pubes for a distance of about 7 cm. Incision of the skin and subcutaneous tissue down to anterior rectus sheath. Infiltration into and below this sheath. Incision of sheath and retraction of muscle bellies. Infiltration of bladder wall and pushing upward of peritoneal reflection. Small incision of bladder wall between guides down to mucosa, which pouts into the wound. Use of aspirating



trocár or catheter to empty the bladder. Incision of mucosa and quick, gentle exploration of the bladder by the finger. Adjustment of a self-retaining catheter in the bladder. Suture of the wound with a small drain of rubber tissue in the anterior vesical space.

**SECOND OPERATION.** *Transvesical Prostatectomy.* General anesthesia by gas and oxygen. Patient in moderate Trendelenburg position, with legs covered by separate blankets, leaving region of anus accessible. Careful reopening of wound in skin and muscles down to the bladder. The finger in the cystotomy opening directs incision of the anterior bladder wall downward to within 2.5 cm. of the prostate. Introduction of self-retaining retractor and wide exposure of bladder neck. Insertion of two fingers of the left hand into the rectum, and with this support the prostate is enucleated from above. With continued support by the rectum, the cavity is packed with kephalin gauze under pressure. Removal of the gauze and control of the bleeding-points by suture. Double layer of interrupted sutures in the anterior bladder wall. Large drainage tube adjusted in the upper angle of the wound. Accurate approximation of structures of the abdominal wall by suture. Hypodermoclysis of 750 c.c. of saline solution.

The factors which lead to the choice of either the perineal or suprapubic form of prostatectomy are therefore seen to be five in number. In the first instance the choice is determined by the condition of the patient and of his bladder and urethra. If it be possible to explore the bladder satisfactorily by the cystoscope and adequate constant drainage by inlying catheter can be instituted for a sufficient period of time the perineal operation will be chosen. It will also be our choice in any case presenting areas of questionable malignancy on rectal palpation. All cases in which the urethral catheter cannot be borne, or those in which the element of infection in prostate, bladder or possibly kidneys is predominant, will demand the suprapubic operation in two stages. It is also wisest to approach all cases showing diverticula or tumor of any considerable size by the suprapubic method, since in many such instances removal of the prostate must be accompanied by excision of the diverticulum or tumor ere the patient be entirely free from difficulty. Stones of any usual size can be removed equally well by either route. And, finally, choice of operation will be determined by the experience of the individual operator in one form or the other of operation, together with his ability or inability to use a cystoscope.

It is my hope and expectation that through the growing recognition by the general surgeon of the principles to be followed in the removal of a prostate the time is not far distant when the operation will have become standardized and the patient thus be offered increased safeguards.

## THE NERVOUS SYMPTOMS IN PERNICIOUS ANEMIA: AN ANALYSIS OF ONE HUNDRED AND FIFTY CASES.<sup>1</sup>

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It was not without some hesitancy that I selected this particular topic, since the literature on the subject is already voluminous, and additional contributions would almost seem unwarranted. A careful review of the subject, however, reveals that many of our pet views concerning pernicious anemia rest on a foundation that is indeed insecure; that there is existing the widest divergence of opinions, some of which may possibly be brought into harmony by facts that may be gleaned from the analysis of a larger number of cases; and that fundamental problems are still left entirely unexplained, the inherent perplexities of which greatly augment our desire to aid in their solution.

"The mind occasionally wanders," said Addison, when, in 1855, he gave to the world his classical description of idiopathic, pernicious anemia. This statement practically summed up what was known of the central nervous system in its relation to pernicious anemia until 1886, when Lichtheim described three cases of the condition, which presented symptoms ordinarily seen in tabes. Although Lichtenstern, two years prior to this, had published an article entitled "Progressive Pernicious Anemia in Tabetics," in which he considered the pernicious anemia to be dependent on the tabes, it was Lichtheim who first recognized the true significance of this syndrome.

The resemblance of these cases, both clinical and particularly anatomic, to tabes dorsalis, is however, only superficial. The changes in the cord have been longest known and studied in great detail. Here the degeneration is seen to begin as small, isolated plaques, with primary involvement, as a rule, of the posterior columns, later of the lateral columns also. These plaques, by confluence and secondary degeneration, ultimately bring about a diffuse and extensive disintegration of the white matter of the cord, known as subacute combined sclerosis. Although the brain was for a long time thought not to be involved in this type of degeneration, investigations of the past four years have revealed definite areas of destruction here also. Nor is pernicious anemia alone responsible for this particular type of subacute degeneration. Among the causes are the leukemias, Addison's disease, probably very severe secondary anemias, diabetes, nephritis, senility and arteriosclerosis, pellagra, tuberculosis, syphilis, leprosy, malaria, typhoid, septicemia,

<sup>1</sup> Presented before the Minnesota State Medical Association, August 29-30, 1918, Duluth, Minn.

scarlet fever, diphtheria, influenza, chronic alcoholism, lead, phosphorus, arsenic—in short, degeneration in the nervous system may be the concomitant of almost any chronic intoxication. And, too, in pernicious anemia it is not the anemia so much as the associated toxin or toxins, that is responsible for the damage done the central nervous system.

The obvious conclusion, after a perusal of so long a list of etiologic possibilities, would be that pernicious anemia forms an etiologic basis in but a small fraction of the cases of combined sclerosis. This is by no means true. Dana estimates this at about 10 per cent.; Taylor at 12 per cent.; von Voss, basing his estimate on published cases of combined sclerosis, found pernicious anemia to be responsible in about one-third of the cases, which is approximately the percentage noted at the Mayo Clinic.

To what extent secondary anemia may be responsible for the production of a combined sclerosis of the cord is by no means established. According to Clark, more of the anemias seen in this relationship are secondary than primary, though, he adds, these changes are usually not looked for in secondary anemias. Bramwell, taking the opposite stand, states that in many of these cases, in which the anemia does not conform to the pernicious anemia type, subsequent development will show it to be so. While we can offer no definite figures in this connection, our experience confirms the latter position. The difficulty of deciding this point is greatly increased when one recalls that in secondary anemia the cause of the anemia may easily be the cause of the combined sclerosis, and that severe anemias in young persons, in whom the anemia is not dependent on some toxic factor, are comparatively rare.

The estimation of cord changes present in pernicious anemia patients is variable and ranges from the general statement that it is present, "not in many cases of pernicious anemia" (White), to percentage estimates of approximately 2.8 (Bramwell); 11.7 (Nonne); 25 (McCrae); 40.9 (McPhedran) and 50 per cent. (Henneberg). Since some of these figures were published, the technic of neurologic examinations has been greatly refined so that more accurate observations are possible. Doubtless the percentage of cases of pernicious anemia presenting evidence of cord involvement is considerably higher than any of the foregoing figures. Of 282 unquestioned and not otherwise complicated cases of pernicious anemia seen at the clinic since 1916, 150 were subjected to a detailed neurologic examination, of which no less than 80.6 per cent. presented indisputable evidence of the destruction of nervous parenchyma.

Approximately 12.7 per cent. of the patients came for the express purpose of seeking relief from symptoms directly attributable to involvement of the nervous system. Chief among these were the paresthesias, especially numbness and tingling of the hands and feet, which were present in about 80 per cent. of all cases, regardless

of whether or not involvement of the nervous system could be demonstrated objectively. This was expressed variously; patients complained that their hands and legs felt dead; that their "legs felt like sticks," or "like wood to the hips," "as though in a cast," or that "the hands and feet felt padded," "like thawing out after being very cold," and "as though the limbs were filled with innumerable ticking watches." In some instances the entire body was numb, again some particular part, as the tongue alone. One patient complained that the buttocks were numb and felt much bigger than normal. Many complained of feeling cold all the time, especially in the feet or in the knees, "as though a draft were blowing on them." In one case the teeth and gums felt so cold as to cause the patient great discomfort. A goodly number complained of burning. Some had sticking, stinging pains in the limbs, as if they had been stung by some insect. One woman repeatedly had her daughter look for glass slivers which she thought must be embedded in her finger-tips. Shooting pains or tingling over a large surface occurs at times when some part of the body is touched, as with cotton or with a pin. Occasionally a patient complains of a girdle pain (2.8 per cent.), or the sensation of a tight band drawn around the knees (1.7 per cent.). A number presented themselves for examination because of inability to control the arms and legs properly. One of these, a conductor, was seriously handicapped in his work because of the difficulty he experienced in selecting the proper coins by the sense of touch.

In the motor field, cramping of the calves occasionally proved to be the source of great discomfort. One patient complained principally of tremor. Another exhibited such marked, choreiform movements that she would repeatedly drop objects and fed herself only with great difficulty. In one instance a hemiplegic attack of three days' duration was seen.

In relation to the cranial nerves, diminution in the senses of smell, taste and hearing was noted. A central scotoma gave one patient great inconvenience. Disturbances of taste are not infrequent; to one patient everything tasted sour; to another, bitter, and a third, with normal mentality, included in her dietary egg shells and soft rocks, which she carefully selected. Symptoms referable to disturbance of the eighth nerve, especially roaring, ringing or thumping in the ears, are very common. Sometimes there is a distressing dizziness, and now and then fainting spells are noted.

As to the relationship between the time of onset of the disease, dating this from the first characteristic symptom and the time of onset of the nervous symptoms, there is nothing constant whatsoever. Thus, a patient may die of pernicious anemia without ever presenting any evidence of central nervous system involvement; on the other hand, the appearance of nervous symptoms may antedate the onset of the anemia, as pointed out by Nonne and Bastianelli. This was true in 1.4 per cent. of our cases, the symptoms

that preceded being usually the parasthesias. In one case, the patient had to resort to the use of crutches and catheterization before any anemia was apparent. The longest time interval noted was thirteen months. The duration of the anemia also showed no definite relationship to the time of onset in the nervous symptoms, though in the cases examined the mean duration of the anemia was 2.2 years and the mean onset of the nervous symptoms ten and one-half months later.

TABLE I.—NEUROLOGICAL DIAGNOSIS BASED ON THE EXAMINATION OF ONE HUNDRED AND FIFTY CASES OF PERNICIOUS ANEMIA, IN 80.6 PER CENT. OF WHICH THE CENTRAL NERVOUS SYSTEM SHOWED INVOLVEMENT.

	Per cent.
Subacute combined sclerosis type of lesion . . . . .	99.2
Posterior sclerosis . . . . .	52.2
Combined sclerosis . . . . .	45.4
Lateral sclerosis . . . . .	0.8
Multiple peripheral neuritis also present . . . . .	4.9
Transverse myelitis with primary optic atrophy . . . . .	0.8

A glance at Table I makes it at once apparent that the type of lesion *par excellence* of the nervous system, as evidenced clinically, is a subacute combined degeneration of the cord, regardless of whether this begins in the posterior or the lateral columns or in both simultaneously, though the columns of Gall and Burdock are in the majority of cases first and most extensively involved.

Primary optic atrophy was seen but once, and, as Collier has emphasized, does not form a part of the picture. Why it should be present in this particular case is difficult to say. Doctor Collier has called attention to the possibility of lues being a factor in these cases. This assumption may be supported here by the finding of a transverse myelitis also, which is certainly uncommon in pernicious anemia, though by no means impossible, yet all other evidence pointing to this complication was lacking.

Of considerable interest is the finding of multiple neuritis, which could be demonstrated in addition to the spinal cord lesion in 4.9 per cent. of the cases. Why a multiple neuritis is not found more frequently at necropsy is a fact rather difficult to bring into harmony with clinical experience, for, as this series shows, a neuritis is not so uncommon. In the vast majority of autopsied cases reported, however, the peripheral nerves were either not studied or no mention was made of them. I have been able to find but 2 cases in the literature in which degeneration was demonstrated in the peripheral nerves at necropsy. Von Noorden reports a case with parenchymatous degeneration in the N. tibialis and N. peroneus and Eisenlohr in the N. Saphenous dexter. Doubtless, careful studies of necropsy material in selected cases would reveal neuritic processes to be more common than seems now to be the case.

While it is obviously impossible to submit detailed reports of all of these cases, Table II represents, in brief, the nervous findings noted in their examination. The various headings have been arranged in order of their importance from a diagnostic standpoint rather than in a sequence which would otherwise be more logical.

TABLE II.—RÉSUMÉ OF FINDINGS IN ONE HUNDRED AND TWENTY-ONE CASES OF PERNICIOUS ANEMIA WITH COINCIDENT INVOLVEMENT OF THE NERVOUS SYSTEM.

SENSIBILITY.		DIMINISHED.		Absent.	
Superficial (tactile, pain, thermal)		42.4			
Deep:					
Joint (toes)		60.0		20.0	
Tendon		12.8		0.8	
Vibration (256 V)		82.4		33.6	
Vibration or joint impaired		92.0			
FUNDUS.					
Pathologic				63.4	
Low-grade retinitis				33.0	
Hemorrhagic retinitis				29.6	
Primary optic atrophy				0.8	
MENTALITY.					
Apathy and somnolence				28.015	
Irritability				9.64	
Memory defects				7.23	
Dementia				2.47	
Emotional instability				3.2	
Depression				3.2	
Psychosis				0.8	
Total				35.2	
REFLEXES.		INCREASED.	DIMINISHED.	ABSENT.	UNEQUAL.
Patellar		39.2	28.8	7.2	14.4
Either patellar or tendo-					
Achillis				24.8	21.6
Tendo-Achillis		23.2	46.4	20.8	11.2
Ankle clonus (sustained)		4.8			
Babinski positive		26.4			
Oppenheim		7.0			
Chaddock		2.4			
Rossolimo		1.6			
Mendel-Bechterew		0.8			
COORDINATION.		IMPAIRED.			
Arms		15.2			
Legs		55.2			
Rombergism		52.0			
GAIT.					
Ataxia		28.8			
Spasticity		4.8			
Spastic-ataxic		8.0			
URINARY CONTROL.		PARTIAL.	COMPLETE.		
Incontinence		8.0	0.8		
Retention		4.0	0.8		
MUSCLES.		INCREASED.	DIMINISHED.		
Tonus (legs)		16.0	10.4		
Power, disproportionately					
impaired, in legs			8.0		
Complete paraplegia			1.6		
Atrophy, localized with fibril-					
lation			0.8		
Choreiform movements			0.8		

The cardinal findings anent the objective evidence pointing to involvement of the nervous system occur in the realm of sensation. Superficial sensibility was found to be definitely impaired in 42.4 per cent. of the cases, excluding those in which the diminution was so slight as to be uncertain (Fig. 1<sup>2</sup>).

As Figs. 1 and 2 illustrate, it varied considerably in degree and was usually most marked over the legs and the buttocks, there being no evidence of dissociation of touch, pain or temperature, such as is seen, for example, in tabes (Fig. 2).

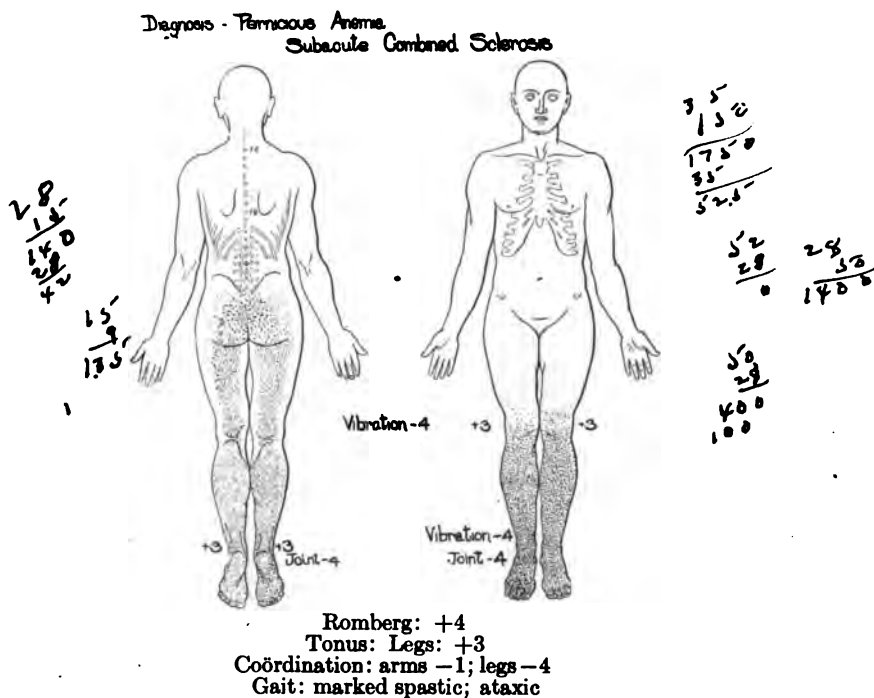


FIG. 1

More significant still is the disturbance of deep sensibility, particularly of vibration and of joint sensibility, which either single or combined were definitely impaired in 92 per cent. Here, too, the disturbance is, as a rule, limited to the legs, pelvis and lower portion of the spine, the upper portion of the body usually escaping intact. It is a rather striking feature that vibration is more frequently and more markedly disturbed than joint sensibility, albeit both forms of sensation are supposed to travel up the cord in fibers which occupy

<sup>2</sup> The numerals used in the figures represent degrees of diminution or increase on a scale of four, 0 being normal, -4 signifying complete absence, +4 very marked increase. Numerals placed next to the figure and not otherwise explained refer to the condition of the reflexes. The stippling indicates diminution in superficial sensibility. Other findings not charted are normal.

relatively the same position in the posterior column. This was very marked in some cases complete absence of vibration sensibility, or pallanesthesia, over the pelvis and legs being noted in 4.8 per cent., where joint sense in the toes was normal. The reverse was never observed to this extent, although in a number of instances joint sensibility was moderately impaired where pallesthesia was normal. The disturbance in deep sensibility is thus seen to be the most outstanding feature in the entire neurologic examination. In only 2.4 per cent. of cases was the disturbance in superficial sensibility more marked than the diminution in deep sensibility.

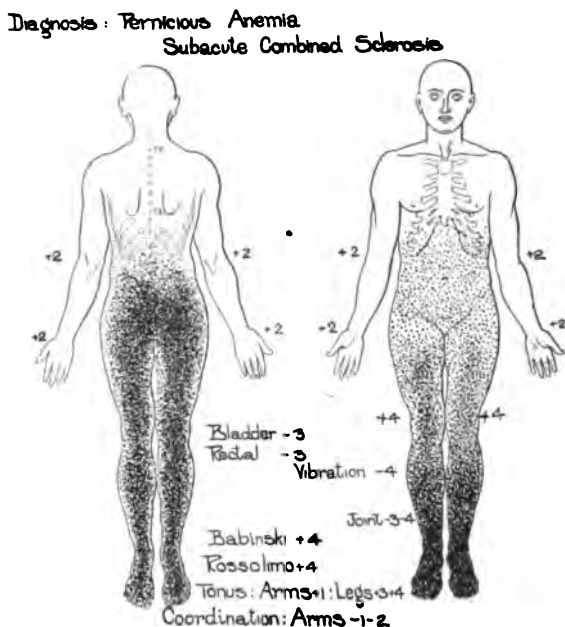


FIG. 2

Within the past few years the psychic phenomena noted in these patients have been exhaustively studied and numerous contributions have appeared, many of them interesting and scholarly, although the texts on psychiatry, on the whole, dismiss the subject with a few remarks or neglect it entirely. A more careful search into the mental condition of these patients would reveal a higher percentage of abnormality than is indicated in Table II, in which only the outstanding features are noted. In only one case was there an outright psychosis present, and this was of the infection-exhaustion type. Here the anemia was ushered in with an acute hallucinatory confusion, which cleared up after three weeks and reappeared once subsequently, *pari passu*, with an aggravation of the patient's physical condition. A number of writers, among them Langdon,



recognize in the psychosis something more or less characteristic, so that a diagnosis of prepernicious anemia has been made in the absence of anemia, which subsequent development of the case confirmed. The majority, however, consider these cases as belonging to the exhaustion type of psychosis, lacking any features which are especially characteristic. Psychoses of the better defined types, such as manic-depressive insanity, are looked on as merely coincident, and have, *per se*, little or nothing to do with the existence of the pernicious anemia.

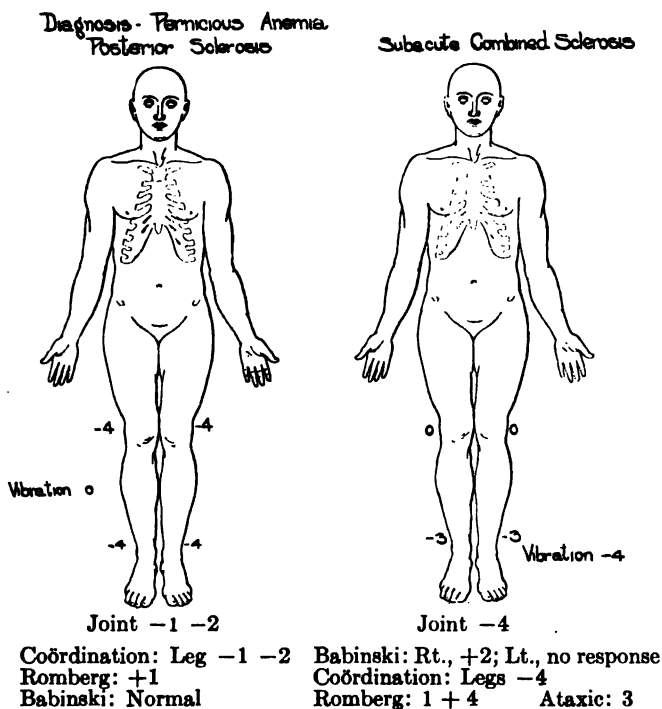


FIG. 3.—On the left, the findings when first seen, on the right, one year and ten months later. Although the knee jerks have returned to normal, due to secondary involvement of the pyramidal tracts, other findings indicate that the degeneration of the spinal cord has progressed and that in spite of a much more satisfactory blood picture.

Relative to the condition of the reflexes, little need be added save in explanation of the chart. The absence of either patellar or tendo-Achillis reflexes, on one or both sides, was noted in 24.8 per cent. and their inequality in 21.6 per cent.

In but one case was there noted a progressive paralysis, with atrophy and fibrillary tremors of the anterior tibial group of muscles on one side, which must be interpreted as a degeneration going on in the anterior horn cells. Doubtless this occurs, though not with the

frequency maintained by Rothmann and Teichmueller, nor yet with the rarity claimed by some of their opponents.

The development of marked choreiform movements in this connection has not, so far as I have been able to learn, been reported before, and is of considerable significance in connection with the pathologic alterations noted in the cerebrum.

Some fourteen years ago a writer on this subject declared that "the study of the spinal cord in pernicious anemia had become an old story." This may be true. The fact remains, however, that our patients still die, and while it may be a long time before any material advance is made in the knowledge of pernicious anemia, our satisfaction with the present status must not act as a shibboleth preventing a better understanding of this disease.

Although the present paper adds little to the knowledge of the condition, I merely wish to emphasize the importance of a correct and early diagnosis in these cases, the prominence which nervous symptoms assume in this disease and the aid which the examination of the nervous system, considering it as a diagnostic measure, may be to the internist.

**SUMMARY.** The salient points of the knowledge gained by clinical evidence of the relation which the nervous system bears to pernicious anemia may be briefly summarized:

In 80.6 per cent. of moderately advanced cases of pernicious anemia there is indisputable evidence of nervous-tissue disintegration. This is in satisfactory accord with the pathologic findings, of which we may take the figures of Minnich, who demonstrated lesions in the spinal cords of approximately 77 per cent. of cases of pernicious anemia. Subjectively, some form of paresthesia, such as numbness and tingling, is rarely missing.

Objectively, one finds the most striking disturbance in the pathologically altered reflexes, not forgetting the tendo-Achillis and Babinski reflexes and the disturbance of vibration and joint sensibilities, the former of which may readily be tested with almost any type of tuning-fork.

As an adjunct in differentiating pernicious anemia from other anemias the examination of the nervous system will be found of inestimable value; it often forms an easy way out of a most perplexing situation.

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## SENSITIZATION AND TREATMENT OF BRONCHIAL ASTHMATICS WITH POLLENS.

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In a recent paper, "A Clinical Study of 400 Patients with Bronchial Asthma,"<sup>1</sup> it was shown to what proteins the patients were sensitive

<sup>1</sup> Boston Med. and Surg. Jour., 1918, clxxix, 288.

and also that such proteins were derived from four chief sources, namely, animal hair, food, bacteria and pollens. In two other more recent papers, "The Treatment of Bronchial Asthma with Proteins,"<sup>2</sup> and "The Treatment of Bronchial Asthma with Vaccines,"<sup>3</sup> three of the chief sources of proteins which cause bronchial asthma were discussed; the former paper discussed sensitization and treatment with the proteins found in animal hair and in food and the latter paper concerned bacteria. The present paper concerns the remaining chief source of proteins, namely, pollens.

This paper will discuss in succession the treatment with pollens "preceding the pollen season," and "during the pollen season," pollens as a possible cause of continuous asthma, the specificity of proteins in the treatment of bronchial asthma in conjunction with multiple sensitization, the association of hay fever with bronchial asthma and the kind of pollens with their respective seasons that are the cause of bronchial asthma.

The method of obtaining pollen from the flower has been outlined in Study XI,<sup>4</sup> and the technic of the skin or cutaneous test which was used to demonstrate sensitization to the pollens has been repeatedly described. Before a patient can be treated with the pollen it is necessary to know how sensitive that patient is to the pollen, therefore different strengths of solutions of the pollen protein are used. These solutions are made as follows: To 0.5 gram of the dry pollen is added 44 c.c. of sterile normal saline and the mixture is shaken thoroughly at frequent intervals for twenty-four hours, after which enough absolute alcohol (6 c.c.) is added to the mixture to make the alcohol content 12 per cent. Again, the mixture is thoroughly shaken at frequent intervals for twenty-four hours, after which the mixture is centrifugalized at high speed and the supernatant fluid is pipetted off and saved. This supernatant fluid therefore consists of the pollen protein dissolved in a 12 per cent. alcoholic-normal saline solution and it represents, by weight, 1 part pollen to 100 parts solvent. This 1 to 100 solution is used as stock and from it other dilutions, 1 to 500, 1 to 1000, 1 to 5000 and 1 to 10,000 are made. These solutions are used for the skin tests and for treatment, and with the addition of a small crystal of thymol they keep for many months in a cool place.

The method of treating with the pollen extracts follows. The first treatment consists of 0.1 to 0.2 c.c. of that dilution next higher than the one which gave a positive skin test, or, in other words, the first dose is 0.1 c.c. or 0.2 c.c. of the strongest dilution which failed to give any skin reaction whatever, no matter how slight. With our pollen extracts the majority of patients whom we treated gave a more or less positive reaction with the 1 to 5000 dilution, therefore the

<sup>2</sup> Arch. Int. Med., 1918, xxii, 466.

<sup>3</sup> Ibid, 1919.

<sup>4</sup> Study XI, Jour. Med. Res., 1917, xxxvi, 237.

first treatment consisted of 0.1 c.c. or 0.2 c.c. of the 1 to 10000 dilution. Treatments were given subcutaneously once a week, and each week the amount of the extract was gradually increased, so that as the treatment progressed, stronger and stronger dilutions were used until one or more doses of the 1 to 100 dilution were given. As an example we will give what we have found by experimentation to be the best outline of treatment for a patient who gives a more or less positive skin test with a 1 to 5000 dilution of pollen extract, and then we will show how we determined upon this outline: 1 to 10000 give 0.2 c.c., 1 to 5000 give 0.2 c.c., 0.3 c.c., 0.4 c.c., 1 to 1000 give 0.2 c.c., 0.3 c.c., 1 to 500 give 0.2 c.c., 0.3 c.c., 0.4 c.c., 1 to 100 give 0.1 c.c., 0.2 c.c., 0.3 c.c., each dose to be given preferably at weekly intervals and never oftener than every five days.

**POLLEN TREATMENT PRECEDING THE SEASON.** By treatment preceding the season is meant that the series of treatments is completed before the season of pollination for that particular plant begins.

For instance, pollination of the plants timothy and redtop, which are the chief causes of early summer pollen asthma, takes place during June and July, so that for these particular plants, treatment must be stopped about the end of May in order to be preseasonal. The most frequent types of summer pollen asthma begin about the middle of August and continue until the first frost, which usually is early in October; this season represents the pollination of the plant ragweed, and it is the ragweed pollen that causes practically all of the pollen asthma at this season. Therefore, treatment with ragweed pollen preceding the season means that treatment must be completed not later than the middle of August.

Thirty-one patients with summer pollen asthma were treated preceding the season. Since in 3 cases the pollens timothy and redtop were the cause of asthma and in the remaining 28 cases the pollen of ragweed was the cause of asthma, treatment with the first 3 cases ceased the end of May, and with the 28 cases treatment ceased just previous to the middle of August; in each group of cases treatment was stopped for all cases at the same time.

Since all patients in each respective group did not present themselves for treatment at the same time the patients varied in the number of treatments they were given, and this variation concerned the stronger strengths of the pollen extract. This was the case because practically all the patients were more or less sensitive to the pollen in a dilution of 1 to 5000, and consequently, with practically all patients, the first treatment was 0.2 c.c. of a dilution of 1 to 10000. Therefore, the chief variation in treatment among the cases was in the number of times the smaller dilutions were given or, in other words, the patients varied in the number of doses of the 1 to 100 and 1 to 500 dilutions which they received.

The following table clearly shows the results of varying the number of treatments with the strong solutions of the pollens:

TABLE I.

Patients.	Last few treat-ments.	Final dilution of pollen extract.	Results.
4	3	1 to 100	No asthma.
7	2	1 to 100	No asthma.
3	1	1 to 100	2 had no asthma, 1 not benefited.
8	3 to 5	1 to 500	5 had no asthma, 1 not benefited, 2 had slight asthma.
5	2	1 to 500	3 had no asthma, 1 not benefited, 1 had slight asthma.
4	1	1 to 500	2 had some asthma, 1 had considerable, 1 not benefited.

In the above table it is noted that all those patients who had two or three treatments with the 1 to 100 solution of pollen were entirely free from asthma during the ensuing season. Of the 3 patients who were given only one treatment with the 1 to 100 dilution, 2 were free from asthma and 1 was not benefited. Of the 13 patients who were given from two to five treatments with the 1 to 500 dilution, only 8 were entirely free from asthma, 3 others had slight asthma and 2 were not benefited. Whereas none of the 4 patients who were given only one treatment with 1 to 500 dilution were entirely free from asthma; although only 1 was not benefited, 2 had "some" asthma and 1 had considerable asthma. Therefore, it is quite evident that in order to prevent asthma caused by pollens by treatment preceding the season, two or three treatments with the 1 to 100 dilution should be given. And although two or more treatments with the 1 to 500 dilution prevented asthma in the majority of cases, the results are so much better when two or three additional treatments are given that the aim should be to continue treatment until two or three doses of the 1 to 100 dilution are given. Patients who received treatment with dilutions no stronger than 1 to 1000 are not shown in the table, because so little treatment is not worth doing.

Since it is evident that two or three treatments with the 1 to 100 dilution are necessary in order to surely protect the patient from having asthma, and since, as already stated, the majority of the patients are more or less sensitive to our 1 to 5000 dilution of the pollens, thus making it necessary to give 0.2 c.c. of a 1 to 10000 dilution of the pollen for the first dose, one must allow for at least twelve treatments as follows: 1 to 10000 give 0.2 c.c., 1 to 5000 give 0.2 c.c., 0.3 c.c., 0.4 c.c., 1 to 1000 give 0.2 c.c., 0.3 c.c., 1 to 500 give 0.2 c.c., 0.3 c.c., 0.4 c.c., 1 to 100 give 0.1 c.c., 0.2 c.c., 0.3 c.c. If the weekly interval between treatments is used it is thus necessary, in the case of the June and July asthma which is caused by redtop and timothy, to begin treatment the middle of March, and in the middle of August

to October type of asthma, which is due to ragweed, it is necessary to begin treatment the first of May.

One might ask if the results would not be as satisfactory if instead of giving a few treatments with each dilution, including the 1 to 100, a large number of treatments were given with the weaker dilution and a fewer number with the stronger dilution. In order to answer this question we will consider three patients in the above table who were not benefited by treatment. One patient was given a total of ten treatments as follows: 1 to 5000, 0.1 c.c., 0.1 c.c., 0.2 c.c., 0.2 c.c., 0.3 c.c., 0.3 c.c., 0.4 c.c., 1 to 1000, 0.1 c.c., 0.2 c.c., 1 to 500, 0.1 c.c.; another was given a total of eleven treatments as follows: 1 to 10000, 0.1 c.c., 0.1 c.c., 0.2 c.c., 1 to 5000, 0.1 c.c., 0.2 c.c., 0.2 c.c., 0.3 c.c., 0.4 c.c., 1 to 1000, 0.2 c.c., 1 to 500, 0.2 c.c., 0.3 c.c., and the third patient was given a total of fourteen treatments as follows: 1 to 10000, 0.1 c.c., 1 to 5000, 0.1 c.c., 0.2 c.c., 0.2 c.c., 0.3 c.c., 0.4 c.c., 1 to 1000, 0.1 c.c., 0.2 c.c., 0.2 c.c., 0.2 c.c., 1 to 500, 0.1 c.c., 0.1 c.c., 0.2 c.c., 0.3 c.c. It is thus seen that a large number of treatments with the high dilutions of the pollen and few or no treatments with the strong dilution are not beneficial. The above 3 cases, however, had to be treated as outlined because each time the dose was increased the patients had soreness at the site of inoculation, thus necessitating the repetition of each dose one or more times. Naturally as such oversensitive cases cannot be foreseen, this is another reason for starting treatment with all cases in plenty of time to allow for such delays.

After the completion of a series of treatments as outlined above, the cutaneous test with the pollens with which treatment has been given is greatly reduced in positiveness. Patients who previous to treatment gave a positive skin test with a 1 to 5000 dilution of pollen protein, give after the completion of treatment a positive skin test with dilutions of the pollen protein no higher than 1 to 100, and the skin test is even less positive than that if several treatments with the 1 to 100 dilution are given. A year later, however, these same patients give practically the same degree of positiveness with the skin test as they did previous to treatment the preceding year. Therefore, the patients become resensitized during the long interval between pollen seasons. This is as one would anticipate, because the patients are not absolutely desensitized; much more treatment would be necessary to absolutely desensitize, consequently the patients prefer to repeat the shorter series of treatments each year.

**POLLEN TREATMENT DURING THE POLLINATION SEASON.** Although, as already outlined, considerable caution must be exercised in the treatment of bronchial asthma due to pollens preceding the season of pollination, in order to avoid shocking the patient from an overdose of pollen, the danger of producing such a result is not great because the patient is not being exposed at the time of treatment to pollens in nature. Treatment with pollens, however, during the

season of pollination must be carried out with the greatest care, since during such treatment the patient is not only being injected with the pollen, but he is at the same time also being exposed to the pollens in nature. Thus there are two chances of erring: the one, the liability of not giving enough pollen to do any good, and the other, by far the more dangerous, the liability of giving too large a dose; not so much that the injected amount alone is too large as that the injected amount, together with the unknown amount which the patient is liable to encounter in nature, may be too large and thus disturbing results may follow the combination. In this method of treatment the skin or cutaneous test is very important and the correct interpretation of the test as regards the proper treatment is most important. The two following cases will illustrate both proper and improper treatment in the same individual.

Case I gave a slightly positive cutaneous test with a 1 to 1000 solution of ragweed pollen. Following a subcutaneous injection of 0.1 c.c. of the 1 to 1000 solution, he was much worse; but a week later following 0.1 c.c. of a 1 to 5000 solution, he was much better—in fact, practically relieved of asthma.

Case II was slightly sensitive by the cutaneous test to a 1 to 1000 solution of timothy pollen. Following a subcutaneous injection of 0.1 c.c. of the 1 to 1000 solution he was so much worse that he refused further treatment for the time being. However, when his asthma returned a month later, it now being caused by ragweed, to which he gave a slightly positive cutaneous test in a dilution of 1 to 5000, a subcutaneous injection of 0.1 c.c. of a 1 to 10000 dilution of ragweed pollen relieved his asthma for several days.

It is thus seen that during the pollen season treatment must be begun with such an amount that fails to give any reaction whatsoever on the skin, and yet if too small an amount is given there will be no benefit. A better testimonial than the above for the value of the skin or cutaneous test as regards the determination of the cause and the treatment of bronchial asthma could not be asked for.

Ten patients who received a sufficient number of treatments during the pollen season, and also were under observation long enough during the pollen season to justify definite conclusions, are presented in Table II.

In Table II it is noted that the first patient, F. L., who was sensitive to ragweed pollen, the second, M. F. M., who was sensitive to both timothy and redtop pollens, and the third, R. S., who was sensitive to timothy pollen alone, were all relieved of asthma by "during the season" treatment with the respective pollens to which they were sensitive. The first and second patients were better following the first dose, and they became free from asthma after the second dose, and the third patient became free after the first dose, and all three continued to be free from asthma throughout the remainder of the season, which varied between four and six weeks. The next two patients, R. H. and M. M., although not entirely



relieved from asthma, had only an occasional slight attack after treatment was begun, and as each patient was treated seven times in seven weeks, they went through practically their whole pollen season with very little trouble. The remaining 5 patients who were treated from four to seven times were not benefited at all; in other words, their asthma continued as usual in spite of treatment. Therefore, of the 10 patients, all of whom were treated exactly alike and very cautiously, 3 were relieved of asthma, 2 were greatly benefited and 5 were not benefited at all by "during the season" treatment. On comparing these results with those obtained by "preceding the season" treatment, as shown in Table I, it is evident that much greater success is obtained by treatment preceding the season than by treatment during the season. Nevertheless, if the former cannot be done the latter is worth trying.

TABLE II.

Patient.	Cutaneous test.	Treatment during season.	Result.
F. L.	Ragweed, 1 to 1000±	1 to 5000 = 0.1 c.c., 0.2 c.c., 0.3 c.c., 0.4 c.c.	Relieved.
M. F. M.	Timothy and redtop, 1 to 500+	1 to 1000 = 0.1 c.c., 0.2 c.c., 0.3 c.c.	Relieved.
R. S.	Timothy, 1 to 500+	1 to 1000 = 0.1 c.c., 0.2 c.c. 1 to 500 = 0.1 c.c., 0.15 c.c.	Relieved.
R. H.	Ragweed, 1 to 10000±	1 to 20000 = 0.1 c.c.; 1 to 10000 = 0.1 c.c., 0.2 c.c. 1 to 5000 = 0.1 c.c., 0.2 c.c., 0.3 c.c., 0.4 c.c.	Slight asthma.
M. M.	Ragweed, 1 to 1000±	1 to 5000 = 0.1 c.c.; 1 to 1000 = 0.1 c.c., 0.15 c.c., 0.2 c.c., 0.25 c.c., 0.3 c.c., 0.4 c.c.	Slight attacks.
S. R. S.	Ragweed, 1 to 5000+	1 to 10000 = 0.1 c.c.; 1 to 5000 = 0.1 c.c., 0.2 c.c., 0.3 c.c.	No benefit.
W. S. T.	Ragweed, 1 to 1000+	1 to 5000 = 0.1 c.c., 0.2 c.c., 0.3 c.c. 1 to 1000 = 0.1 c.c., 0.2 c.c.	No benefit.
T. S. R.	Timothy, 1 to 10000±	1 to 20000 = 0.1 c.c.; 1 to 10000 = 0.1 c.c., 0.2 c.c. 1 to 5000 = 0.1 c.c., 0.2 c.c., 0.3 c.c. 1 to 1000 = 0.1 c.c.	No benefit.
F. G. K.	Timothy and redtop, 1 to 500+	1 to 1000 = 0.1 c.c., 0.2 c.c.; 1 to 500 = 0.1 c.c., 0.2 c.c.	No benefit.
S. M. V.	Timothy, 1 to 1000±	1 to 5000 = 0.1 c.c., 0.2 c.c., 0.3 c.c. 1 to 1000 = 0.1 c.c., 0.2 c.c.	No benefit.

The question now arises: Should both methods of treatment be employed in the same patient provided the treatment preceding the season fails? The answer is in the affirmative, as shown by the following 2 cases who were a part of Table I. One of these patients was not benefited by four treatments with the 1 to 500 dilution of the pollen (see Table I); his asthma began at the usual time, so that treatment "during the season" was then tried. He was given at weekly intervals ragweed pollen in a dilution of 1 to 10000, 0.1 c.c., 0.2 c.c., 0.3 c.c., then 1 to 5000, 0.2 c.c., and 0.2 c.c.; after the third treatment he became free from asthma and continued to be

free through the remainder of the season. The other patient who was not benefited by one treatment of the 1 to 100 dilution (see Table I) preceding the season was given a 1 to 5000 dilution 0.1 c.c., 0.2 c.c., 0.3 c.c., 0.4 c.c., at weekly intervals during the season. For five days following each treatment he was free from asthma, but for the succeeding two days of each interval he had asthma as usual. It should be noted that although both patients had had a number of treatments preceding the season, including the dilutions of 1 to 5000, 1 to 1000 and 1 to 500, when treatment was continued during the season the dose or amount of each treatment was dropped back to that which was first used, namely, 1 to 10000 in the first case and 1 to 5000 in the second case. In other words, they were treated during the season just as though they had not been treated preceding the season. One might ask why this was necessary and why not continue throughout the season, gradually increasing the dose from where the treatment preceding the season left off? The following case (and others might be cited) will show that it is not advisable to give a few treatments preceding the season and then continue increasing the dose through the season. This patient, who was given one treatment of the 1 to 500 dilution and not benefited (see Table I), was continuously treated with gradually increasing amounts throughout the season, with no benefit, and probably the patient had worse asthma than usual. Therefore, a few treatments preceding the season is not advisable. This is probably because the patient is getting large amounts of the pollen in the treatment and at the same time is getting considerable pollen from natural sources, and the combination of the two is sufficient to overcome whatever desensitization has been accomplished by the treatment given preceding the season.

Therefore, in the treatment of pollen asthma there are only two methods available: the best method is to give sufficient treatment preceding the season of pollination and then stop, and by sufficient treatment is meant to begin treatment three months ahead of the season, so that the few final treatments will be with the strongest dilution of the pollen protein (that is, our 1 to 100 dilution). If this method happens to fail, treatment may be continued through the season, but the dosage must not continue on the increase from the amount last given; the dosage must be dropped back to the original first dose and very cautiously increased. The only other method worth doing is not to give any treatment preceding the season but wait until the patient begins to have asthma, then treat cautiously; first give one or more doses of the highest dilution which fails to give any reaction whatsoever on the skin and very slowly increase the succeeding doses. It is far better to give two doses that are so small that no improvement results before a beneficial amount is given than to run the risk of giving too large an initial dose, which may upset the patient and thus discourage the physician.

**POLLENS AS A POSSIBLE CAUSE OF CONTINUOUS ASTHMA.** Frequently, patients who have asthma more or less continuously throughout the year give a history of onset of asthma or of their first attack during some summer month when some flowers are pollinating, and they also give a positive cutaneous test with the pollens of that particular season. Frequently the relationship between pollens and continuous asthma is even more suspicious; each year the patient begins asthma during a pollen season, but the asthma does not stop when the season of pollination is over; instead the asthmatic condition persists for several months or until the first seasonable spring weather the following year. Such a patient will then be well until that particular pollen season occurs again; the patient is sensitive to the pollens occurring during that season. The following case well illustrates the sequence of events in this type of asthma. The patient has had hay fever and asthma for nineteen years, and she gives a positive cutaneous test with ragweed pollen in a dilution of 1 to 5000. During the first few years the patient had hay fever and asthma from the middle of August to the first of October, thus being at that time a typical ragweed pollen case. A few years later the asthmatic condition would continue until December, although the hay fever would stop as usual in October. A few years later still the asthmatic condition continued until spring, the hay fever still ceasing as usual. During the past two years the asthmatic condition has continued the year round, although she only has hay fever as usual from the middle of August to the first of October. Other cases in whom the pollens are less suspiciously a cause of continuous asthma give a history that their asthma, although continuous throughout the year, is much worse during certain summer months, and they give positive skin tests with the pollens which are prevalent at that particular time.

Table III includes 14 cases which are instances of the above, and in 7 of these the relief from asthma following treatment with the pollens confirms the belief that pollens were the primary cause of asthma.

TABLE III.

Patient.	Onset.	Positive skin test with pollens.	Duration.
1. Miss B.	July	Timothy, redtop and ragweed	Throughout year.
2. Miss L.	July	Timothy, redtop and ragweed	Throughout year.
3. Mrs. G.	August	Ragweed	Throughout year.
4. Mr. T.	August	Ragweed	Throughout year.
5. Miss W.	August	Ragweed	Throughout year.
6. Mr. G.	August	Ragweed	Throughout winter.
7. Mr. F.	August	Ragweed	Through November
8. Mrs. M.	August	Ragweed	Throughout winter.
9. Mr. S.	August	Ragweed	To December.
10. Mr. P.	August	Ragweed	To December.
11. Mr. A.	August	Ragweed	To November.
12. Mrs. S.	August	Ragweed	To November.
13. Mrs. O'L.	August	Ragweed	Throughout winter.
14. Mrs. M.	August	Ragweed	Throughout winter.

The above group of cases needs little explanation. The first 2 patients began to have asthma in July; they were sensitive to the summer pollens—one was always worse in summer—and, although the asthma continued throughout the year, pollens were suspected as the primary cause of the asthma. The next 3 patients are similar to the first 2, with the exception that the first attack of asthma occurred during August, when ragweed pollen is in season, and consequently ragweed pollen may be suspected as the primary cause of asthma. The remaining patients are similar to the 3 just discussed, with the exception that asthma did not continue all the year, but instead it stopped at various times during the winter; in the last 2 cases it is most suspicious that ragweed primarily caused asthma, since during the first few years the asthma was confined to the months of August and September, which is the season of ragweed pollination. So much for the supposition as based upon history. Fortunately we have had the opportunity through pollen treatment of confirming our belief that pollens were the primary cause of asthma in some of these cases. These treated cases will be discussed in the following paragraph:

The first patient (Miss B.) in Table III, whose asthma began in July, who has always been worse in summer and who was sensitive to the pollens of timothy, redtop and ragweed, has had two of the best summers—in fact, has had very little asthma—following a series of treatments with the pollens to which she was sensitive.

Patient No. 8 (Mrs. M.) was treated with ragweed pollen, to which she was sensitive, and following treatment she had no asthma as usual during August and September, neither has she had any asthma during the winter; previous to this she has had asthma as shown in Table III for over thirty years.

Patient No. 9 (Mr. S.), who has had asthma for five years, from the middle of August to December, and was sensitive to ragweed pollen, had no asthma at all for two years following a series of ragweed treatments given each year for these two years; the next year no ragweed treatment was given, and he had asthma as usual.

The remaining five patients (Nos. 10, 11, 12, 13, 14) were all quite similar in that they all had had asthma for years from August to or through the winter months; they were all sensitive to ragweed pollen, and following ragweed treatment they all were entirely free from asthma during the ensuing fall and winter. Therefore, these 8 patients who were free from asthma following treatment with the pollens to which they were sensitive would seem to definitely establish the fact that pollens were the primary cause of asthma in such cases, and that surely such patients should be treated with the pollens to which they are sensitive on the chance that they may be relieved of asthma.

The question now arises, Why does not the asthma in such cases stop when the pollen season terminates, or, in other words, what

prolongs the asthma after the primary cause ceases to exist? The answer is that various other causes prolong the asthma, and one of these is bacteria as a secondary invader. Six to eight weeks of continuous severe asthma may cause so much local irritation in the bronchial tree that the field is fertile for secondary bacterial invasion, and in addition the patient's general resistance has been lowered. In Table III, Cases No. 6 (Mr. G.), No. 9 (Mr. S.) and No. 12 (Mrs. S.) represent such an instance. Case No. 6 was not treated with pollen, but after the pollen season was over treatment was begun with his autogenous sputum vaccine, and he gradually became free from asthma until entirely so after three or four doses; this same procedure was repeated a second season, with the same good results, although for the previous seven years without treatment the asthma continued all winter. Cases Nos. 9 and 12 were similarly treated, with equally good results, the year preceding that in which pollen treatment was given.

TABLE IV.—SPECIFICITY OF PROTEINS IN THE TREATMENT OF BRONCHIAL ASTHMA.

Patient.	Duration of asthma.	Positive skin test.	Treatment and remarks.
1. M. A.	August to October	Ragweed	Vaccine no benefit; ragweed pollen relieved.
2. H. B.	June to July	Pollens slight	Pollens no benefit; vaccines relieved.
3. A. G.	Throughout year	Ragweed slight	Ragweed no benefit; vaccines relieved.
4. D. M.	Throughout year	Ragweed slight	Ragweed no benefit; vaccines relieved.
5. J. M.	Throughout year	Ragweed	Ragweed relieved in summer; vaccines relieved in winter.
6. R. S.	Throughout year	Early and late pollens	Pollens relieved in summer; vaccines benefited in winter.
7. I. G.	Throughout year	Ragweed, S.P. albus	Ragweed relieved in summer; vaccines of S.P. albus relieved in winter.
8. R. W.	Throughout year	Timothy: horsehair	Timothy relieved in summer; horsehair proteins relieved in winter.
9. C. S.	Throughout year	Timothy: horsehair	Timothy relieved in summer; horsehair proteins relieved in winter.
10. W. G. T.	Throughout year	Ragweed: horsehair	Ragweed relieved in summer; horsehair proteins relieved in winter.
11. M. M.	Throughout year	Redtop; timothy; horsehair	Pollens relieved in summer; horsehair proteins relieved in winter.
12. M. P.	Throughout year	Ragweed	Ragweed relieved the complication of hay fever but asthma not benefited.

Other causes which may prolong a pollen asthma, or, in other words, other causes which together with pollens produce a more or less continuous asthma, are included in Table IV under the title,

**Specificity of Proteins.** We have shown in previous papers that in the treatment of bronchial asthma there is a specificity of proteins, but pollens have not been included in this connection; also, the question of multiple sensitization or multiple causes of asthma in the same individual has been discussed without particular reference to the pollens. Therefore, although the chief reason for presenting Table IV is to illustrate the specificity of proteins in the treatment of bronchial asthma, the cases also illustrate multiple sensitization and various causes for the prolongation of pollen asthmas.

In Table IV the first patient (M. A.) who had asthma during the ragweed pollen season and who was sensitive to this pollen has been under observation three years. The first year treatment with a vaccine of *Staphylococcus pyogenes aureus*, while he was having asthma, had no effect on his condition; the next year he was treated, preceding the season, with ragweed pollen, and he had no asthma; last year he was not treated at all and he had asthma as usual. The second patient (H. B.), who had had asthma for five years only during June and July, and was only slightly sensitive to the pollens corresponding to that season, was not benefited one year by treatment either preceding or during the season with those pollens, but the next two seasons he was relieved by autogenous sputum vaccines. The next two patients (A. G. and D. M.) are so similar that they may be considered together. Both patients, who had had asthma for seven years continuously throughout the year and were only slightly sensitive to ragweed pollen, were treated preceding and during the season with ragweed pollen without benefit; treatment, however, with autogenous sputum vaccines relieved the asthma in both cases and they remained free from it while under vaccine treatment, which has been given to them off and on for the past two years. Therefore, these 4 cases illustrate the specificity of proteins in the treatment of bronchial asthma; the first case was strongly sensitive to ragweed pollen, and treatment with it prevented asthma (specific treatment); however, treatment with vaccines did not benefit (non-specific treatment); the remaining 3 cases were so very slightly sensitive to pollens that pollen treatment was not indicated, therefore the pollen treatment which these patients were given was non-specific and not beneficial; following vaccine treatment, however, these patients were relieved. The latter 3 patients bring up the question how strongly positive must be a reaction to pollens to indicate pollen treatment; this will be discussed later on in this paper.

The next 2 cases in Table IV, namely, J. M. and R. S., may be considered together. Both were positive with pollens and pollen treatment preceding the season prevented both from having asthma during the pollen season; nevertheless, their asthma returned during the winter. Treatment with autogenous sputum vaccines, however, relieved one patient entirely of asthma; the other patient was

greatly benefited. These 2 cases definitely show the specificity of treatment, and like those patients presented in Table III, they illustrate the importance of pollen treatment in those patients who are definitely sensitive to pollens even though such patients have asthma after the pollen season is at an end.

The next five patients in Table IV, namely, I. G., R. W., C. S., W. G. T. and M. M., are similar. All were sensitive to pollens, and pollen treatment prevented asthma during the pollen seasons; but during the remainder of the year they had asthma as usual. These patients were, however, sensitive to other proteins—Case I. G. to *Staphylococcus pyogenes albus* and the other patients were sensitive to the proteins of horse dandruff, and treatment with these proteins relieved and prevented the winter asthma which they had been having for periods varying between eight and seventeen years. These patients not only illustrate the specificity of proteins in the treatment of bronchial asthma, but also multiple sensitization and the necessity of treatment with more than one type of protein in such cases; furthermore, such cases confirm the value of the skin or cutaneous test.

The last case (M. P.), in Table IV, had asthma throughout the year and hay fever from the middle of August to the first frost; she was sensitive to ragweed pollen. Treatment with ragweed pollen preceding the season prevented her from having her customary fall hay fever, but her asthma was the same as usual. Therefore, the pollen treatment explained the cause of hay fever but not the cause of asthma, and thus the patient had two separate conditions from different causes at the same time. This is another instance of specific protein treatment, of the specific value of the cutaneous test and of the necessity of treatment as determined by the skin test, in order to rule out all possible causes of bronchial asthma. This case also brings up the association of hay fever with bronchial asthma.

**ASSOCIATION OF HAY FEVER WITH BRONCHIAL ASTHMA.** In this paper have been included only those patients who had bronchial asthma throughout the whole or greater part of the respective pollen season. For instance, many such patients had asthma throughout the season, many others had asthma after a few days of hay fever, then both continued throughout the season and the remainder had hay fever for ten days to two weeks before asthma began, then both continued throughout the season. Frequently, hay fever patients have a very slight attack of asthma at some time during their hay fever, often the hay fever symptoms end with a day or two of asthma and still others are more or less choked up at times during their hay fever. None of the latter cases are included in this paper because the amount of asthma was too slight and the attacks too unreliable to claim benefit or relief from treatment. These cases do, however, show the frequent association of hay fever and asthma when caused by pollens.

Of the 31 patients in Table I who were treated preceding the season, 27, or all but 4, had hay fever with their asthma; of the 10 patients in Table II who were treated during the season, 7, or all but 3, had hay fever with their asthma; and two other similar typical pollen asthmas, who were presented in this paper, to show the necessity of carefully selecting the proper dose of pollen, also had hay fever with their asthma. Therefore, of the typical pollen asthmatics, in 80 per cent. hay fever was associated with asthma and both conditions were caused by the same pollen as shown by pollen treatment.

Among the 14 patients in Table III there were 8 who also had hay fever, and of the 10 patients in Table IV who had asthma throughout the year 2 had hay fever. In the whole series of 600 asthmatics, excluding those who are included in this paper, there were 12 who had hay fever. Therefore, a positive cutaneous test with pollens in patients who have bronchial asthma may mean that those patients have pollen hay fever and that the pollens play no part in the cause of asthma; the only way to tell is to treat with the pollens which give positive tests.

Eleven patients who had bronchial asthma and who are not included in this paper gave positive cutaneous tests with pollens in dilution no stronger than 1 to 500; 5 of these gave a positive test in a 1 to 100 dilution and the remaining 6 patients gave positive tests with the 1 to 500 dilution. As a general rule it seems unnecessary to treat such cases with pollens, especially if the patients are sensitive to other proteins, because in the experience we have already outlined they are probably not sufficiently sensitive to pollens to have much trouble from them. In the last four paragraphs entitled "The Association of Hay Fever with Bronchial Asthma," the 92 patients who, in a former paper,<sup>5</sup> were shown to be sensitive to pollens have thus all been accounted for.

**THE POLLEN SEASONS AND THE POLLENS THAT CAUSE BRONCHIAL ASTHMA.** There are three definite pollen seasons. The first occurs in April and May when the various trees pollinate; among the first to pollinate during this season are the willow, birch and maple and the last one to pollinate is the pine, which occurs the last day or two in May. Although the pollen of any of these trees may cause asthma, we have had only one case caused by willow, one by birch and one by pine pollen. Since the length of time which each tree requires to complete pollination is no longer than two weeks, and in the case of the pine tree only one day, it is quite unnecessary to treat these patients for such a short exposure to the pollen.

The second pollen season, and a more important one, occurs during June and July. The principal plants which pollinate at this time are the rose, June grass, orchard grass, redtop and timothy;

<sup>5</sup> Boston Med. and Surg. Jour., 1918, clxxix, 288.



the latter two are also grasses and are familiarly known as hay. We have not had a case of asthma caused by the rose, although there are such on record; neither have we found orchard grass to be a cause; these two plants surely are not frequently a cause of asthma. June grass is so similar botanically to redtop that we do not use it in our tests. The important plants in this group are redtop and timothy grasses, and of these two timothy is the chief cause of bronchial asthma at this season. Practically every patient who was sensitive to timothy was also somewhat sensitive to redtop, but usually less so. In our series of cases redtop never gave a stronger reaction than timothy; in only 5 cases did both pollens give an equally strong reaction and in only 1 other case did redtop give a test nearly as strong as did timothy; in the 8 remaining cases included in this paper redtop reacted little or not at all, while timothy gave a strong reaction. (The adjectives qualifying reaction refer to various dilutions of the pollen protein; for instance, an equally strong reaction means that both pollens gave a positive test in the same high dilutions, and referring to the latter part of the previous sentence concerning the 8 remaining cases it is meant that these cases gave a positive skin test with high dilutions of timothy, whereas with redtop the patients either gave negative tests or positive tests with only very low dilutions.) Patients who were equally sensitive, or nearly so, were treated with both pollens, but those who gave positive tests with high dilutions of timothy and with concentrated dilutions of redtop were treated only with timothy pollen extract. A fair idea may be obtained regarding the frequency of these pollens as a cause of asthma by referring to Tables I and II, which included definite cases of seasonal pollen asthma; of the total of 41 cases, in 8 the pollens of redtop and timothy were the cause of asthma; this percentage of frequency, however, is a little too high for a large series of cases.

The third pollen season, and by far the most important, occurs during August and September, and the important pollens at this time are those of ragweed, golden rod and daisy. The daisy really begins to pollinate in July and finishes in early September; golden rod pollinates during August and September and ragweed usually begins to pollinate about the middle of August and ceases with the first heavy frost, which usually occurs early in October. Ragweed is practically always the cause of pollen asthma at this season, and in only one case have we found the daisy the cause, and in one other was golden rod the cause. These three plants belong to the same botanical family, although they are not intimately related to each other, and consequently every patient that reacts positively to one need not react to all. The proportion of positive skin reactions among these three pollens is brought out by the patients presented in Tables I and II. Of the 41 patients presented in the two tables, in 32 the asthma was caused by ragweed pollen alone and in one

other both ragweed and daisy pollens were the cause. This shows how much more frequently ragweed pollen causes bronchial asthma than the next most common pollens that cause it, namely, redtop and timothy. Of the 32 patients who had asthma from ragweed pollen, 3 gave a positive cutaneous test with ragweed pollen protein in a dilution of 1 to 10000, 21 with a dilution of 1 to 5000 and 8 were positive with a dilution no stronger than 1 to 1000. These same patients gave skin tests with the pollens of the daisy and golden rod as follows: 6 were negative with the whole pollen of golden rod and 5 with the whole pollen of the daisy, 5 were positive with the whole pollen of golden rod but negative with a 1 to 100 dilution, and with the whole pollen of the daisy one was positive, 13 were negative with golden rod diluted 1 to 100, but whole pollen was not tested and 15 were negative with the daisy diluted 1 to 100, but whole pollen was not tested; 7 other patients were positive with golden rod pollen extract in a dilution of 1 to 100 but negative with higher dilutions, and 6 were positive with the daisy pollen extract diluted 1 to 100 but negative with high dilutions; 2 patients were positive with golden-rod pollen in a 1 to 500 dilution and 3 were positive with daisy 1 to 500; no patients were positive with golden-rod pollen extract in dilutions higher than 1 to 500, whereas with daisy pollen extract 2 were positive with 1 to 1000 dilution and one with 1 to 5000 dilution. Since the above patients were treated only with ragweed pollen, to which they were most sensitive, with the exception of the one patient who was equally sensitive to both ragweed and the daisy and was treated with both, it is evident that in practically all patients who have pollen asthma during August and September ragweed is the cause.

Attention should be called to the fact that some patients have so-called asthma during June and July, others during August and September and still others have so-called asthma throughout the summer; but they are not sensitive to pollens, and the asthma in these cases is caused by bacteria; a series of these cases was reported in a previous paper.<sup>6</sup> Therefore, it is essential to do the skin or cutaneous test in all cases of summer asthma, and it is just as ridiculous to treat all summer asthmatics with pollens. Furthermore, it is unnecessary and possibly harmful to treat pollen asthmatics with an extract composed of many pollens, such as in the past has been put on the market by commercial firms, when the patient actually requires only one or possibly two varieties of pollen. Attention should also be called to the fact that occasionally the pollen seasons vary in time, depending upon weather conditions. For instance, during the summer of 1918 June grass pollinated in May, red top and timothy were still pollinating in August and ragweed began to pollinate the first week in August. Naturally these

<sup>6</sup> Arch. Int. Med., 1919.

seasons also vary with localities. What has been written in this paper holds for Massachusetts, but farther north the seasons are retarded and farther south the seasons are ahead of this schedule. Furthermore, the same pollens are not found in all localities. There are places in New Hampshire where ragweed does not grow; in Florida there is no ragweed, but golden rod grows in abundance; in the South and middle West the grass alfalfa abounds, and, as shown by Selfridge,<sup>7</sup> none of the eastern pollens are found in California. Therefore the ridiculousness of treating summer asthmatics over the whole country with the same pollens, as in the past some commercial houses have advocated, is quite evident and the necessity of doing skin or cutaneous tests is just as evident.

In conclusion, readers of this paper should bear in mind that we collected our own pollens and made our own preparation by the method already outlined and that our results depend upon these facts. Our results will naturally be specifically true only when our methods are followed or with those who purchase the individual pollen preparations which are comparable with our own. Otherwise, our results will hold only in a general way as regards the degree of sensitiveness of the patient and the amount of treatment necessary.

**CONCLUSIONS.** Patients who have seasonal bronchial asthma caused by pollens are prevented from having asthma by a series of treatments with the pollens to which they are most sensitive provided sufficient treatment is given, and by this is meant a series of treatments consisting of various dilutions of the pollen protein ranging from the strongest dilution which fails to give a positive cutaneous test to the strongest dilution which gives a positive test. When our methods are used the usual proper treatment is as follows: 1 to 10000 give 0.2 c.c., 1 to 5000 give 0.2 c.c., 0.3 c.c., 0.4 c.c., 1 to 1000 give 0.2 c.c., 0.3 c.c., 1 to 500 give 0.2 c.c., 0.3 c.c., 0.4 c.c., 1 to 100 give 0.1 c.c. 0.2 c.c., 0.3 c.c.

Treatment with pollens during the season is less reliable, but worth doing provided much treatment preceding the season fails or cannot be given. In such cases very small amounts of the pollen protein should be given.

<sup>7</sup> Spasmodic Vasomotor Disturbances of the Respiratory Tract, with Special Reference to Hay Fever, California State Jour. of Med., April, 1918.

Other papers on the study of bronchial asthma made possible through a gift by Mr. Charles F. Choate, Jr., of Boston, to the Peter Bent Brigham Hospital are as follows:

Studies I-V, Jour. Med. Research, 1917, xxxv, 373, 391, 487, 497, 509.

Studies VI-VIII, Jour. Immunol., 1917, ii, 227, 237, 243.

Study IX, Am. Jour. Bot. July, 1917.

Studies X-XIII, Jour. Med. Research, 1917, xxxvi, 231, 237, 243, 295.

Study XIV, *ibid.*, xxxvi, 423.

Study XV, *ibid.*, 1917, xxxvii, 51.

Studies XVI and XVII, *ibid.* 1917, xxxvii, 277, 287.

Study XVIII, Jour. Am. Med. Assn., 1918, lxx, 897.

The Cause and Treatment of Bronchial Asthma, Med. Clinics of North America, Boston, 1918, i, No. 4.

Asthma caused by pollens may continue after the termination of the pollen season. The continuation of asthma in these cases is due to secondary bacterial infection, causing bronchitis in a patient whose resistance, either local or general, has been lowered because of prolonged, severe pollen asthma.

Patients who have continuous asthma throughout the year should be treated with pollens if they give positive cutaneous tests with them, in order to determine whether or not the pollens may in part be a cause of asthma. The association of hay fever with bronchial asthma is so common in pollen cases, and is sufficiently frequent in continuous asthma to warrant pollen treatment in all patients who are sensitive to pollens.

The most common pollen that causes seasonal asthma is that of ragweed, whose season of pollination extends, as a rule, from the middle of August to the first frost, or about the first of October. The next most common pollens to cause asthma are those of redtop and timothy, usually both together, but of the two, timothy is the more frequent cause. These, however, are poor seconds to ragweed pollen. The season of pollination of redtop and timothy is during June and July. Rarely the pollen of various trees which pollinate during April and May, the pollen of the rose during June and July, the pollen of the daisy during July and August and the pollens of corn and golden rod during August and September are the cause of bronchial asthma.

## REVIEWS

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**SURGICAL TREATMENT.** By JAMES PETER WARBASSE, Formerly Attending Surgeon to the Methodist Episcopal Hospital, Brooklyn, New York. Volume 1. Pp. 899; 699 illustrations. Philadelphia and London: W. B. Saunders Company, 1918.

THE author here presents the first volume of a large three-volume work on surgical treatment. Judging the prospective two volumes by this one, we recognize a very ambitious effort and one worthy of the tremendous amount of work it has required. The outstanding feature is that it is a one-man production in contrast to the usual system of surgery by many authors. The one-time common and popular text-book of surgery by one author seems to have lost its hold on the profession, with a few noteworthy exceptions. Even the large systems by many authors, most of whom work and write along special lines, do not seem to maintain their popularity through more than a few editions, evidently because they cannot keep abreast of the important advances in surgery. The progressive surgeon must be familiar with the original literature as it appears in the journals. Even in the matter of surgical treatment alone, one not infrequently fails to realize how difficult it is to condense this amount of material, or the best of it, into the narrow confines of three volumes. Whatever their defects, such books are very essential in the life of the busy surgeon for ready reference and reasonably reliable guidance, and there is much to be said for this unusual one-man system. Duplication and overlapping of subjects is largely avoided. Many noted writers on special branches of surgery have displayed much difficulty in determining what the average physician and general surgeon need most. Warbasse shows not only a remarkable capacity for absorbing the literature himself, but for presenting its essential features in such a form that the ordinary reader may absorb it also.

A striking general feature is the wide area covered with a noteworthy attention to detail. In view of the great number of surgical contributions, due to the war needs and irrespective of the war, the author displays an unusual ability to be brief, comprehensive and clear in his summaries of this material. The general excellence of the work and of the numerous illustrations make it difficult to particularize concerning individual features. The reviewer, however,

cannot agree with the author in all things. He would criticize, for instance, Fig. 215, on page 365, which shows digital pressure being made on the femoral artery about under the spine of the pubis instead of under the middle of Poupart's ligament. All surgeons will not agree that "ordinarily the reduction of a fracture is simple and satisfactory." A skiagraphic illustration of a fracture of the shafts of say both bones of the leg, with considerable overlapping of the fragments before reduction, and a similar illustration of the same fracture showing reduction of the deformity would have been more convincing. Diagrammatic illustrations do not satisfy. Compressing the artery supplying the bone, the use of drugs or of anemia by the ischemic rubber bandage, to aid the reduction by relaxing the muscles, will not appeal strongly to the experienced surgeon. That fractures of the greater tuberosity of the humerus and of the head and neck of the radius are rare is not supported by the roentgen-ray evidence. Fig. 475, on page 633, is evidently copied from one which appeared elsewhere a few years ago, and its reappearance is unfortunate. It illustrates an operation for recurrent dislocation of the shoulder that never was done and never will be, because the anatomical conditions illustrated do not exist. To the uninitiated it is alluring, but if followed will prove bitterly disappointing.

But these are trifles in a great mass of up-to-date, readily digestible, well coördinated, surgical therapeutic facts, very valuable and necessary to the practising surgeon. The author is to be congratulated on the magnitude and importance of the work he has accomplished. The surgeon and practising physician are also to be congratulated because of the opportunity it affords of finding what they need most of modern surgical knowledge so arranged and illustrated that it is readily accessible. T. T. T.

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FORCED MOVEMENTS, TROPISMS AND ANIMAL CONDUCT. By JACQUES LOEB, Member of the Rockefeller Institute for Medical Research. Pp. 209; 42 illustrations. Philadelphia: J. B. Lippincott Company, 1918.

THIS is the first of a projected series of monographs on general physiology and experimental biology by American writers. It is now thirty years ago since the author of this book put forward his well-known theory of tropisms or forced movements in regard to animal behavior. The idea was first suggested to him by observing the behavior of plants, such as stems bending toward the light of a window or the growing ivy stem inclining toward a solid support. By careful experimental procedures he found the behavior of lower animals to be similarly governed by external forces. To these forces he applied the same terms as had been used in plant physi-

ology, as heliotropism, galvanotropism, geotropism, etc. In the interval since the idea was first advanced many investigators have worked upon the lines which the author then indicated. This is attested to by the 554 references to literature at the end of the book. These and the discussion of their results, which the book contains, will serve as a source of collected information and of reference to all those interested in the subject. W. H. F. A.

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THE HUMAN SKELETON. AN INTERPRETATION. By HERBERT E. WALTER, Associate Professor of Biology, Brown University. Pp. 214; 174 illustrations. New York: The Macmillan Company, 1918.

To those whose early study of the human skeleton was coincident with the first strenuous months of their medical education, this simple presentation will serve to give a new viewpoint. Instead of time-honored descriptions and hackneyed expressions, the author uses every-day language in his attempt to inject life into the dry bones. Perhaps some may disapprove of his partly humorous method of handling scientific facts. His interpretation is largely based upon evolutionary lines, or, to use one of the author's own expressions, "the present skeleton is only the latest model," and is bound in the future to undergo many modifications. To show the directions in which the various parts of the skeleton are evolving, he draws largely upon comparative anatomy and embryology. The result is a readable book, in which the more general and larger aspects of the subject are emphasized to the exclusion of much of the usual minutiae. W. H. F. A.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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**Post Malarial Severe Anemia.**—HARRINGTON and WHITELAW (*Glasgow Med. Jour.*, June, 1918, No. 51) state that shortly after their arrival in Macedonia they were impressed by the occurrence after malaria of cases of grave anemia, apparently of the pernicious type. It was found possible to examine 80 cases, involving 121 full blood counts and complete physical examinations. With the exception of a few Bulgar and German prisoners the patients were all Serbian soldiers. For the differential results, five hundred cells were counted. (1) *Severe Forms:* (1) Post-malarial anemia may assume a grave type characterized by all the signs and symptoms of pernicious anemia but without evidence of oral or intestinal sepsis. (2) The spleen is enlarged, sometimes considerably so, but the liver is seldom enlarged. (3) The blood shows marked diminution of red corpuscles, high color index, leukopenia with a relative increase of lymphocytes and to a lesser extent of large mononuclears, poikilocytosis, megalocytosis, polychromasia, occasional granular basophilia, the presence of megaloblasts and normoblasts, and a small percentage of myelocytes frequently, and myeloblasts constantly. (4) Such cases occur most frequently as a sequel of subtertian malaria, but may follow benign tertian. (5) Recovery usually follows prompt and energetic treatment, but death may occur, and the gravity of the prognosis increases with the age of the patient. (6) Treatment by arsenic used as in pernicious anemia, either as liquor arsenicalis in increasing doses, or galyol or kharsivan intravenously, usually leads to recovery. It should be combined with treatment by quinine, orally or



intramuscularly as indicated. (II) *Mild Forms*: (1) The blood shows a less marked diminution of red corpuscles, a low color index except in a few more recent cases, a less marked leukopenia with a relative increase of lymphocytes, and large mononuclear cells, slight poikilocytosis, occasional megalocytes and polychromasia, rarely granular basophilia, the presence of normoblasts and rarely of megaloblasts, and a small percentage of myelocytes frequently, and of myeloblasts constantly. (2) The average age of the patients is lower. (3) Recovery is the rule.

**The New Treatment for Paralysis Agitans.**—SWIFT (*Boston Med. and Surg. Jour.*, November 21, 1918, No. 21, clxxix, 644) cites briefly the treatment of three typical cases of a method which consists solely in the muscular movements of a simple nature, gone through very slowly, at the rate of about one foot to the second, with strong mental concentration upon the movement while it is in progress. First come movements of the right foot, then of the left, then of the legs successively, then of the right and left arms in order, then of both arms, and finally of the hands and fingers. The object is not muscular development but rather development of nervous control over the muscles. The movements should be regular and they should be definitely prescribed, but it is not necessary to outline any special form for them in this place because they can easily be invented by anyone. No particular value need be attached to any special set of exercises, because the nervous control is the same in one as in another. It seems likely that the essence of the entire treatment lies in this slowness of movement, and perhaps also in the mental concentration which should accompany the movement. The purpose of these exercises is to develop just this feeling of pervading steadiness to such a pitch that it endures as a constant feature of the patient's physical life. By my own experience with them and by my observation of patients' use of them I am led to believe that these exercises do build up a central inhibitory control.

**The Bacillus Influenzæ in Sinusitis and Meningitis.**—LACY (*Jour. Lab. and Clin. Med.*, November, 1918, No. 2, iv, 55) reports case histories and postmortem pathological and bacteriological findings in two cases of influenzal meningitis in infants and the clinical and bacteriological findings in two cases of frontal sinusitis in young men. He concludes: In all cases of meningitis, either mild or severe, of indefinite etiology it is advisable to centrifuge the spinal fluid and culture it on various media, always using blood agar. Observations on this should be made for at least forty-eight hours before a negative report is made. The presence of Gram-negative bacilli in direct smears or on cultures from cerebrospinal fluid or from the accessory sinuses of the respiratory tract should be looked upon as probable *Bacillus influenzae*. This is especially true when long filamentous forms are present. There are probably two types of *B. influenzae* as suggested by the cases reported here: the one which retains its original short bacillary form indefinitely on artificial media and the other which readily develops filamentous forms after a few days on moist blood agar. Sinus infections with the *B. influenzae* should have early and adequate drainage to prevent the danger of a complicating meningitis. *Note.*—Since the completion of the above work, Major H. E. Robertson, of the American Expedi-

tionary Force in France, has reported the recovery of *B. influenzae* from the accessory sinuses of 14 cases at autopsy: 7 times out of 8, cases of influenzal tracheobronchitis; 6 times from patients dead from other infectious diseases; and 2 from men dying of accidental causes. Major Robertson did not go into the cultural characteristics nor morphological differences of the bacillus.

**A Study of the Neutralization Properties of Antipoliomyelitic Horse Serum.**—NUZUM (*Jour. Infect. Dis.*, September, 1918, No. 3, xxiii) says that antipoliomyelitic horse serum prepared by repeated intravenous injections of the coccus isolated from the central nervous system in human and monkey poliomyelitis possesses neutralizing properties against the virus of poliomyelitis. Immune horse serum protected 11 monkeys perfectly against fatal doses of virus. In two monkeys in which both immune human serum and immune horse serum failed to neutralize the virus, a definite delay of sixteen days in the onset of paralysis must be attributed to the immune horse serum as compared with a shorter delay of eleven days with immune human serum known to possess much neutralizing principles. The neutralizing properties of antipoliomyelitic horse serum *in vitro* for the virus of poliomyelitis afford a convenient and satisfactory test of the potency of this serum for use in the treatment of poliomyelitis. Suitable controls with normal horse serum and comparisons with immune human serums known to possess neutralizing properties should be conducted simultaneously. Finally, the neutralizing, protective and curative properties of antipoliomyelitic horse serum for experimental poliomyelitis of monkeys are in direct accord with the favorable results observed in the serum treatment of human poliomyelitis and argue strongly for the etiological relationship of the coccus to this disease.

**Report of Epidemic of "Spanish Influenza" Which Occurred at Camp A. A. Humphreys, Va., during September and October, 1918, by I. W. Brewer, M.D., Geneva, N. Y., Lieutenant-Colonel, M. C., N. A., Camp Surgeon, Camp A. A. Humphreys, Va.**—(*Jour. Lab. and Clin. Med.*, December, 1918, No. 3, iv, 87). In a detailed analysis of the report of the so-called "Spanish Influenza," well illustrated by graphic charts, the author analyzes the statistics concerning incidence of the disease and its complications in the various regiments. He considers the distribution and time of occurrence of the cases, the relation of dust and weather to the spread of infection, the incidence among colored organization, and concludes that (1) the incidence of the disease increases with the density of population in barracks. (2) That the hanging of a sheet between the individual beds in the barracks was of value in preventing infection. (3) That the negro race suffered much less from the disease than did the white. (4) That there were more cases complicated with pneumonia among the colored troops and that the disease was more fatal among them.

**The Clinical Pathology of Mustard Gas (Dichlorethylsulphide) Poisoning,** by GEORGE R. HERRMANN, M. S., M.D., Ann Arbor, Michigan.—(*Jour. Lab. and Clin. Med.*, November, 1918, No. 2, iv, 1). This writer concludes: (1) that mild cases of mustard gas burns of the

skin show no changes in the blood or urine. (2) Moderately severe and severe cases of mustard gas burns of the skin with some involvement of the upper respiratory tract show after the first week definite changes in urine, blood urea and blood. (3) The urinary changes consist in a diminution of the urinary output, increased concentration and acidity, albuminuria, and diminished urea and chloride output. In the sediment there may be found casts, renal epithelium, red blood cells and an increased number of leukocytes. Under forced fluids prompt improvement occurs. (4) Coincident with these urinary changes the blood urea is found to be high, but approaches normal with the improvement in the urinary condition when fluids are forced. (5) The blood shows a slight secondary anemia with a well-marked polymorphonuclear leukocytosis, a definite eosinophilia, and the appearance of myelocytes and young forms of leukocytes. The blood platelets were usually increased. No evidence of hemolysis was found. These changes indicate a disturbance in the white cell formation rather than in the red blood cell group. No leukopenia was noted at any time. The leukocytosis reached its height coincidentally with the height of the secondary infection and fell with the improvement of the infection. (6) The temperature, pulse and respiration charts show in the severe cases an initial period of shock. With the development of the necrosis and the secondary infection there is a corresponding febrile reaction. (7) The bacteriological examination of the infected skin lesions and furuncles showed constantly the presence of *Staphylococcus pyogenes aureus*. In the one bronchial cast obtained streptococci were present. (8) We believe that the changes in the blood and urine may be interpreted as dependent upon the secondary infection and, in part, possibly, to the absorption of toxic products from the necrotic skin, rather than to any direct toxic action of mustard gas.

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## THERAPEUTICS

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UNDER THE CHARGE OF

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**An Experimental Investigation of the Cause of Early Death from Arsphenamine and of Certain Other Features of the Pharmacological Action of the Substance.**—In the present series of experiments, JACKSON and SMITH (*Jour. Pharm. and Exp. Therap.*, 1918, xii, 221) have investigated the mechanism of acute death following the administration of arsphenamine. They studied especially the effects of various preparations of arsphenamine on the cardiovascular system with a view of discovering the cause of the acute reaction often seen in the clinic. They report that the slow injection of therapeutic quantities of arsphenamine in very dilute alkaline solution produces no striking results in anesthetized dogs. However, as the rate of injection and the concen-

tration of the drug are increased, toxic symptoms soon become manifest. The earliest of these symptoms consist in a dilatation of the heart, perhaps mainly of the right side at first; a progressively increasing pulmonary blood-pressure, and a slow, gradual, but not severe, fall of systemic pressure. The cause of the rise in pulmonary arterial pressure is believed to be due partly to the alkalinity of the solutions of arsphe-  
namine used, and partly to the specific action of the drug itself. While the authors have not been able to prove that the formation of emboli in the pulmonary vessels may not be in part responsible for the increased pulmonary pressure, they believe that no such action as this occurs. With large, toxic doses, the right heart may have to contract against a pulmonary pressure increased by 100 per cent. above the normal, while at the same time the left ventricle may be contracting against a systemic pressure reduced by 25 to 50 per cent. below normal. These peculiar conditions may tend to establish a state of increased irritability and instability in the heart, and in rare instances may lead to delirium cordis. Drugs of the epinephrin type tend to increase the instability of the heart under these conditions. The reactions of the internal organs when arsphe-  
namine is injected are variable. Apparently both central and peripheral influences are concerned. As a rule, oncometric tracings of the spleen and intestinal loop show a dilatation, while the kidney usually contracts, sometimes most vigorously. The toxicity of arsphe-  
namine is not increased by the breathing of high concentrations of carbon dioxide nor by the injection of calcium hydroxide, calcium lactate or of monosodium phosphate. A number of intermediate compounds, occurring during the process of manufacture of arsphe-  
namine, were also studied. None of these is very poisonous and none can account for the variable toxicity of the different samples of arsphe-  
namine, which may or may not contain traces of one or more than one of these. The authors suggest that in those cases in which severe, acute, toxic symptoms suddenly manifest themselves, either during or shortly after the intravenous injection of arsphe-  
namine, tyramine is more likely to be of benefit to the patient than is any other drug with which they are acquainted.

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**The Application of a Concentrated Solution of Magnesium Sulphate to Scalds and Burns.**—MELTZER (*Jour. Pharm. and Exp. Therap.*, 1918, xii, 211) reports that burns of the first and second degree are invariably arrested in their development when molecular solutions of magnesium sulphate have been applied early. Third degree burns run, as a rule, a more favorable course under the application of magnesium sulphate than under any other treatment. Higher concentrations than 25 per cent. seem to exert a still better influence. The favorable action of the application of magnesium sulphate in advanced stages of burns of the second and third degree is less striking, especially on account of the infection present, but even then it seems to exert a favorable influence and ought to be used in combination or alternatingly with antiseptics.

## GYNECOLOGY

UNDER THE CHARGE OF

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**Magnesium Sulphate Solutions in the Treatment of Spastic Contractures of the Rectum and Sigmoid Colon.**—Through repeated sigmoidoscopic and roentgenologic studies, SOPER (*Am. Jour. Med. Sc.*, 1918, clvi, 205) has found that spastic contractures of the lower colon and rectum of varying intensity play an important part in the etiology of many cases of chronic constipation and of the gas pains and abdominal distention following operations on the abdomen and pelvis. The most frequent site for these contractures is the rectosigmoid juncture, severe contractures at this point presenting a syndrome described by the writer as "sigmoido-spasm." A most obstinate form of constipation, he finds results from combined contractures and dilatations, *e. g.*, (a) atony of the rectum and sigmoid associated with contracture at descending colon; (b) contraction at the rectosigmoid angle and atony of the sigmoid loop; (c) contracture at the splenic flexure and descending colon and atony of the cecum. The contractures, he feels, are the result of disturbances in Meltzer's law of contrary innervation, a predominance of stimulation occurring in the exciting or contractile phase. Reasoning on the basis of Meltzer's experimental work, which showed that solutions of magnesium sulphate produce an inhibitory influence upon peristaltic movements of the intestinal tract when the salt is given intravenously or applied directly to the mucosa, the writer has applied a saturated solution of magnesium sulphate directly to the contractures in a series of 220 cases. He applied the solution by means of cotton applicators through the sigmoidoscopic tube (knee-chest position), a diffuse, pink color appearing in the mucosa within from ten to twenty seconds. Mild contractures disappeared in a few seconds. Moderate contractures required a minute or two, and in order to relax strong spasms a series of applications were necessary. Of 80 cases of obstinate constipation, 68 cases were apparently completely restored to a condition of normal colonic function. The number of treatments required in these cases varied from ten to thirty applications given every second or third day. Five cases were complicated by inflammatory induration and distortion of the bowel at the rectosigmoid junction, consequently treatment was ineffectual. In 7 cases the contractures were overcome, but normal colonic function was not restored. Of 72 cases of obstinate spastic constipation, *i. e.*, cases that were of long standing but that had not been previously under his care, 64 were successfully treated, with satisfactory restoration of bowel function. Eight cases were extremely neurotic individuals who could not stand the treatment, although no real pain is produced by it. Sixty-eight cases of obstinate spastic constipation, cases of long-standing constipation, but which presented contractures that were moderate in character, *i. e.*, that readily responded to treatment and required but from six

to ten applications to restore good colonic function. The patient is asked to return for treatment every second day, the interval between treatments being gradually lengthened. All purgatives and water enemata are discontinued; an oil enema may be used if the patient is unable to come for treatment at the proper time. If the contracture cannot be reached through the sigmoidoscope, two ounces of the solution may be injected by passing a soft-rubber catheter through the sigmoid tube. Roentgenological examination in a series of 6 cases of postoperative abdominal distention and gas pains showed that the colon alone was involved; sigmoidoscopic examination showed the presence of marked contractions in the rectum and lower sigmoid. In a series of 30 such cases an enema of saturated solution of magnesium sulphate was given according to the following technic: Three ounces of saturated solution of magnesium sulphate is introduced by means of the rectal tube passed four or five inches into the bowel, elevating the hips whenever possible and having it retained as long as possible. This procedure may be repeated every day or several times a day if so desired. There was immediate relief in 24 cases. While the enema was usually retained only about five minutes, there were no toxic effects when it was retained for twenty-four hours.

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**Rational Preoperative Treatment, with Special Reference to Purgation.**—In a recent paper PEET (*Jour. Am. Med. Assn.*, 1918, lxxi, 175) has pointed out the many advantages of the simple enema over the various forms of pre-operative catharsis so widely employed. The administration of cathartics on the night preceding operation is followed almost invariably by loss of sleep, psychic and physical weakness, loss of body and intestinal fluids, change in the bacterial flora of the intestine, hypotonicity of the intestinal wall and irritability of the rectum and lower colon. Postoperative thirst after such a preparation must necessarily be greater, and because of the higher degree of irritability of the rectum, thirst cannot be relieved by the easiest and safest method. It is impossible, even with a powerful purgative, to eliminate all the intestinal products which might lead to putrefaction, since waste products are continuously passing into the intestines. Moreover, attempts at sterilization by calomel and other drugs, the writer feels, are useless. While many organisms are carried out, there is a tendency to change in the bacterial flora, usually in the direction of multiplication of fermentative organisms. Clinical evidence favors a change to the simple enema. For the past six years a careful study was made of patients receiving pre-operative catharsis and those receiving the simple enema only. In the latter cases postoperative thirst, nausea and vomiting occurred much less frequently, and the patients were in much better mental and physical condition at the time of the operation.

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**Is the Purgation of Patients Before Operation Justifiable?**—On the basis of an extensive clinical and experimental study, ALVAREZ (*Surg. Gynec. and Obst.*, 1918, xxvi, 651) goes a step further than the previous article and advocates that even the simple pre-operative enema be avoided unless absolutely necessary, that food be given as late as possible before operation, that water and solid food be given by mouth as soon after operation as possible and that purgatives should be abso-

lutely avoided both before and after operation. The writer sums up his reasons for avoiding purgatives before operations as follows: (1) Some of the purgatives owe their effects to the fact that they are irritant poisons that must be removed quickly from the body. Others act by interfering with intestinal absorption and by upsetting the balance of salts. In either case they bring about pathological conditions. The body is weakened and not strengthened. (2) We know now that the dehydration of the body and the upset in salt balance are bad, particularly before an operation in which there may be hemorrhage and vomiting. (3) With magnesium sulphate there may be an increased amount of fluid in the bowel to disturb those who want it empty. In operations on the colon, liquid contents are more difficult to control mechanically than are solid masses. (4) There is an increased growth of bacteria. There is some evidence that there is an increased absorption of toxins, and a greater permeability of the mucous membrane to bacteria. Undigested food may be carried down into the colon to supply increased pabulum for the bacteria. (5) By weakening some parts of the bowel and making others more irritable the even flow of material from stomach to anus is rendered impossible. (6) Whether from disturbances in motility, in absorption, in the circulation or in the bacterial conditions there certainly is a tendency to flatulence and distention. (7) When the bowels must move frequently during the night the loss of sleep is considerable. The purgation is particularly trying if the patient is wearing a large cast, has a broken leg or other painful lesion which makes each resort to the bedpan an ordeal. (8) If the patient should happen to have some intestinal obstruction, a gangrenous appendix, a badly diseased Meckel's diverticulum or adhesions forming around some pus, purgation may directly cause death. (9) Purgation makes the bowel react so poorly to drugs that there may be grave difficulties in meeting postoperative emergencies. (10) Emptying the bowel by starvation and purging makes the resumption of colonic activity much more difficult. The colon must be filled and distended to a certain extent before it will empty. (11) The fact that children and nervous women will sometimes begin vomiting during the night, before the operation, shows that the purge must be responsible for some of the postoperative nausea and vomiting. The ether adds the finishing touches to what was begun the night before. These conclusions were reached as the result of a series of experiments on purged animals conducted by the writer and F. B. Taylor. They studied the effects of castor oil, magnesium sulphate, cascara, calomel and tincture of jalap on rabbits by excising segments of the intestines from five different points, placing them in warm oxygenated Ringer's solution and noting changes in the gradients of rhythmicity, irritability or latent period. Only mildly laxative doses were used; the drugs were given at noon and the animals killed next morning. The bowels were found injected, full of fluid and gas, sometimes atonic and flabby, often irritable here and there and inclined to contract down into hard white cords. When the segments were placed in Ringer's solution their contractions were weak and irregular and they soon became fatigued. One of the most important points noted was the diminished sensitivity to the local application of drugs, some having to be increased one hundred times. Magnesium sulphate appeared to be the most objectionable from the surgical standpoint,

since by preventing the absorption of water it causes great distention of the bowels with fluid. Calomel and cascara did not cause such pronounced signs of poisoning and fatigue in the excised segments as did castor oil, magnesium sulphate and jalap. The segments from the calomel rabbits beat well with a large amplitude and slow regular rhythm. The gradient of rhythm showed irregularity only in the animals that had received castor oil. The latent periods of the segments showed marked deviations. Some segments showed an abnormally high degree of irritability with a very short latent period, others scarcely respond to the strongest current. Normally the latent periods are graded from short ones in the duodenum to longer ones in the ileum. The engorgement of the mesenteric vessels and the injection of the intestinal wall were quite sufficient to upset the delicate balance between the gases in the intestine and those in the blood. Besides omitting the purgative the night before, the writer suggests that if the operation is not to be performed earlier than 10 A.M., a light breakfast may be eaten, although in occasional cases, of course, fear and apprehension may lengthen the emptying time of the stomach. Enemata should be given only to those who are definitely constipated or who are to have an operation on the lower colon or on the pelvic organs. Furthermore, gas-oxygen should have preference over ether whenever possible, as its effects on the digestive tract are much less. The importance of giving solid food as soon as possible after operation is strongly emphasized by the writer, because of its tonic effect on the tract, but cellulose should be avoided. The postoperative use of purgatives is quite as bad as their pre-operative administrations.

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**Vertigo of the Menopause.**—Although vertigo is seldom the only prominent symptom of the menopause, since it is almost always accompanied by such disturbances as hot and cold flashes, cold perspiration, palpitation, blurred vision, flickering before the eyes, headache, nausea, etc., nevertheless it is one of the most interesting phenomena that occur at this important time of life and has been the subject of investigation by SANES (*Am. Jour. Obst.*, 1919, lxxix, 7). Like most other investigators who have studied this condition, he attributes the vertigo to a lack of the internal secretion of the ovary and most of his contribution has to deal with the question of treatment. Before any plan of treatment is decided upon, one must make sure that the case is one of climacteric vertigo. Such pathological conditions as lesions of the internal ear or of any other part of the balance mechanism, such diseases as cardiovascular, renal and ocular, especially muscular unbalance of eyes, must be excluded. If the case can be definitely diagnosed as that of climacteric vertigo, the treatment must always be that of the menopause in general. As the metabolism is almost always below par in the menopause, the nutrition and elimination of the patient must be looked after and, as the insufficiency or absence of the ovarian internal secretion is the underlying cause of the symptoms, ovarian organotherapy is logically indicated. Sanes reminds us however, that we do not know the active principle of the internal ovarian secretions; in fact, we do not even know definitely which part or parts of the ovarian substance (Graafian follicle, corpus luteum or the interstitial cells) is responsible for the internal secretion. It seems plausible there-



fore, that if by the administration of glandular tissues we can successfully replace a deficiency in internal secretion of the gland, the whole ovarian substance, in the present state of organotherapy, should meet best the needs of a menopause patient. For this reason Sanes prefers using the whole ovarian substance in the treatment of climacteric disturbances in general and vertigo in particular. There is one difficulty that is met by those who prescribe glandular extracts and that is the lack of standardization of the preparations. One must specify the name of the manufacturer or the proprietary name of the ovarian preparations to get the dosage desired, since one manufacturer will base the dosage of an ovarian preparation on the quantity of the *fresh* ovarian substance in it, while other manufacturers will base their product on the amount of *desiccated* substance contained. Sanes uses a preparation of ovarian extract, each grain of which represents a grain of the fresh ovarian substance, the dosage being 5 grains two to four times a day. Larger doses were only occasionally found to be of any more benefit than the small doses routinely used. In this study, the records showed that about 37 per cent. of the cases were improved, while in 25 per cent. there was complete control of the vertigo by using the ovarian extract. In an occasional case, the addition of a small dose of thyroid extract to the ovarian extract seemed to have been a benefit.

**Pathology of Chronic Metritis.**—Chronic metritis and chronic subinvolution of the uterus are two gynecological conditions, which, until recently, have been considerably confused and although these terms are frequently used by practitioners, they are frequently used interchangeably and many times when the user has a hazy conception of the condition that he is describing. It might be worth while then, to glance at the conclusions reached by SCHWARZ (*Am. Jour. Obst.*, 1919, lxxix, 63) in a rather extensive study of this subject. He states that chronic subinvolution alone is by far the most frequent cause of enlarged uteri, causing hemorrhage, pain or leucorrhea. The thickness of the uterine wall is due, in order of their importance, to an increase of the elastic tissue, edema and liquefaction of the connective tissue and hypertrophy or enlargement of the individual cells. Chronic metritis as a true inflammatory condition does exist and is frequently responsible for the symptoms in these enlarged uteri. However, chronic metritis locally is never a primary disease, but is secondary to chronic endometritis, chronic salpingitis or chronic inflammation within the pelvis. It should be remembered that chronic subinvolution and chronic metritis may coexist in the same uterus. Chronic pelvic inflammation is only occasionally seen in connection with chronic subinvolution and therefore other factors must play a greater role in the production of this condition; for example, in Schwarz's series of 38 cases, there were only 6 that showed inflamed appendages and only 7 had chronic endometritis. Schwarz believes that the term "chronic metritis" should be abolished from the clinical standpoint. The term chronic subinvolution might be substituted in cases of multiparous uteri, which are definitely enlarged, and cause symptoms without evidence of pelvic inflammation. This would probably include over 80 per cent. of the uteri which, pathologically show signs of chronic subinvolution. The term chronic metritis might be applied to those cases in which there

is evidence of pelvic inflammation in connection with a more or less immovable uterus. This would, in all probability, embrace a greater portion of cases of true chronic metritis, as well as those in which there is a distinct overlapping of both conditions. In addition to placing a majority of these cases, clinically, in a class descriptive of their pathology, there is another advantage of using the term chronic subinvolution, since the frequency of its occurrence will be constantly impressed upon the observer. The condition, of necessity, must result from a lack of involution of the puerperal uterus, therefore its prevention lies in the proper care of patients during pregnancy labor, and the puerperium.

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## OPHTHALMOLOGY

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**Ocular Affections in Typhoid.**—DANTRELLE (*Inaugural Thesis, Annali, D'Oculist*, October–November, 1918, p. 529) has studied ocular manifestations observed during an epidemic of typhoid fever. He classifies them as symptoms and complications. *Symptoms:* Conjunctival hyperemia occurs ordinarily with the rise in temperature, frequently intense, it continues at times during the entire febrile period and occasionally even during defervescence. The frequency of this symptom is shown by the fact that during an epidemic many cases are sent to the ophthalmic departments with the diagnosis of acute conjunctivitis when the case is one of typhoid fever. Subconjunctival ecchymoses of the size of a head of a pin to that of a pea are frequently observed upon the course of a subconjunctival vessel, and occupying the inferior cul-de-sac or the bulbar conjunctiva near the limbus. Ciliary alopecia is inconstant; it sometimes accompanies alopecia of the hairy scalp. Myosis occurs as does also photophobia. The fundus frequently presents slight hyperemia of the papilla which recovers entirely. *Complications:* Complications are observed in about 1 per cent. of the cases; Dantrelle has noted 65. He divides them into those due probably to the unknown organism of the disease; these are quite rare, the others occur during convalescence and are caused by adventitious infections. Cataract (7 cases) begins on the tenth to the fifteenth day of the disease; it is accompanied by discoloration of the iris; as the subjects are usually young, the cataract is soft. Alterations of the fundus (11 cases) consist either in papillary lesions or in those of the retinal circulation. These lesions are characterized by a vascular pigmentation; the pigment surrounds the arterial or venous branches forming a pigmented network upon the vessels; they are accompanied

by grave and definite functional disturbances. The papillary lesions are simple atrophy following optic neuritis. Ocular palsies (3 cases) of the third or sixth pair have occurred during the height of the affection. As complications of convalescence, the author notes palpebral abscess, orbital phlegmon, corneal ulcers, optic atrophy following erysipelas, or phlegmon of the orbit. These late complications are due to the streptococcus; antistreptococcic serotherapy appears to be of some service.

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**Acute Anterior Ethmoiditis in Young Subjects.**—STEPHENSON (*British Jour. Ophthalm.*, No. 8, ii, 416) writes that in his experience a form of unilateral orbital inflammation or suppuration is not infrequent in young children under five years of age, although its essential nature is not always recognized. Many of the milder cases recover spontaneously with or without a discharge of pus from the nostrils or into the nasopharynx. A certain number of cases are diagnosed at a later stage as orbital cellulitis, as shown by tenderness, edema and redness of the eyelids, chemosis and protrusion and impaired motility of the eyeball, which is usually displaced downward or downward and outward. General symptoms, such as fever, headache, vomiting, etc., are usually present in the more severe cases. As a rule, there is no history of injury, or of erysipelas, or any other local or general malady or illness. The reporter believes that this group of cases can be best explained by an acute inflammation of the anterior ethmoidal cells: in certain of the more severe cases the posterior ethmoidal cells may also be involved. The condition is not accompanied by any ophthalmoscopic nor rhinoscopic signs. Recovery is the rule under the simplest measures. When symptoms are severe, or the general condition of the patient is threatening, surgical measures must be adopted: an incision into the orbit over any spot which seems to indicate underlying pus. If nothing escapes, the dressing forceps, with closed blades, are introduced into the depth of the wound, and the blades of the instrument are then more or less widely separated; pus may make its appearance two or three days later. The writer has adapted as a routine measure a somewhat different procedure, which consists of raising the bone over the region of the anterior ethmoidal cells when pus usually escapes. The prognosis is favorable.

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**Blood Cysts of the Orbit.**—GIFFORD (*Am. Jour. Ophthalm.*, September, 1918, p. 625) concludes that in every case of deep-seated orbital tumor of uncertain nature the possibility of blood cyst and some other benign cyst should be considered. If an operation is done the tumor, on being exposed, should be secured by passing a thread through it and its nature tested by puncture. If it proves to be a cyst, thorough cauterization with phenol or something similar should be tried before an attempt is made to extirpate it.

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**Observation of the Fundus During Temporary Blindness.**—ORMOND (*British Jour. Ophthalm.*, May, 1918, p. 273), during an attack of ephemeral amblyopia, observed in the fundus four or five distinct notchings of the inferior retinal vein, which suddenly disappeared, with simultaneous return of the vision; the pupil, which was enlarged during the

crisis, became contracted. The reporter thinks the condition to have been due to contraction of a central artery entailing pallor of the disk and surrounding retina, with a diminution of blood in the vein, causing the endothelium of the vein to become wrinkled into horizontal folds as the vessel became empty. Neither cardiac, vascular nor renal disease was demonstrated.

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**Tuberculin in Ocular Disease.**—VERHEYDEN (*British Jour. Ophthalm.*, April, 1918, p. 223) finds that tuberculin gives good results in phlyctenular kerato-conjunctivitis, especially as regards photophobia, blepharospasm, lacrimation, but does not prevent relapses, although the latter when they occur are milder; the usual local treatment is also employed. Scleritis and episcleritis are more rebellious; the other etiologic factors of these affections should be eliminated before having recourse to tuberculin. One case of iridocyclitis, probably bacillary, recovered by local treatment and six injections of tuberculin. One case of paralysis of the third pair, of tubercular origin, with double ptosis, paralysis of the right superior rectus and slight diplopia, recovered after a relapse during the course of the treatment, which consisted of six injections of tuberculin (0.001 to 0.009) made during an interval of nine months.

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**A New Sign of Death.**—LECHA-MARZO (*Archiv Med. Belg.*, March, 1918, p. 271) calls attention to a sign of death applicable in civil life as well as upon the battle-field. It consists in placing a piece of turmeric paper upon the globe under the lids; in life, slight pressure gives a bluish spot, but no change in color is observed in the cadaver; in fact, the red color at times appears more pronounced. In the living, ocular acidity is never observed; immediately after death the reaction is slightly alkaline as in life, shortly after death the reaction is neutral and finally acid. This ocular acidity makes its appearance almost uniformly during the eight hours following death.

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## PATHOLOGY AND BACTERIOLOGY

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UNDER THE CHARGE OF

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**Method of Collecting Blood for the Wassermann Test.**—WANG (*Jour. Path. and Bact.*, 1918, xxii, 85) advocates a simple method for collecting the patient's blood for the Wassermann reaction. The blood is collected upon pieces of filter paper about the size of a dime. This blood can easily be obtained as a drop from the finger or the lobe of the ear. He estimates that each drop collected in this way upon the paper contains 0.04 c.c. of serum. Upon collection, these small pieces of paper

are allowed to dry and then are used in the regular system for carrying out the Wassermann reaction. Each paper represents a unit of patient's serum. In place of the measured fluid serum the slip of paper is added to the series of tubes. He claims that the results are very satisfactory and it is quite easy to standardize the individual systems to give satisfactory results with this mode of collection. He points out that this method has great convenience for obtaining blood in private houses when other facilities are not at hand.

**Agglutination Reaction of the Meningococcus Against Carriers.**—Since the beginning of the War in 1914 much importance has been laid upon meningococcus carriers. The determination and segregation of individuals having pathogenic meningococci within the nose became of great importance for the prevention of meningitis among the soldiers. Various methods have been advocated for the determination of the meningococci. During the first two years, the recognition of this organism from other Gram-negative cocci was carried out by cultural tests upon carbohydrates (dextrose, levulose and saccharose). VINES (*Jour. Path. and Bact.*, 1918, xxii, 56) compares the results of the analyses of the first two years with those of the third year when the determination of the Gram-negative organisms was carried out by serological tests. By this means organisms which are morphologically similar were divided into four groups. His analyses showed that the number of carrier cases among the troops has increased, while the number of cases of meningitis also became greater. It was also demonstrated that various types of Gram-negative cocci may be present in the nasal secretion at the same time. Some of these types can be separated by the fermentation reaction while others are recognized only by the serological test. It was found, moreover, that certain cases periodically showed the presence of meningococci with intermissions of negative cultures. In these it is suggested that the source of infection may lie in the sphenoidal sinus which periodically discharges them. The author believes that certain spontaneous variations may occur in the agglutination reaction of the meningococci in the nasopharynx.

**Encephalitis Lethargica.**—For several months past reports have appeared in England and upon the continent of cases of botulism, hemorrhagic poliomyelitis and encephalitis. Gradually it was recognized that these various reports were referring to a common condition which is being discussed under the heading of encephalitis lethargica. MOTT (*British Med. Jour.*, 1918, ii, 488) discusses the cerebral lesions. Punctiform hemorrhages were found in the neighborhood of the floor of the fourth ventricle, the third ventricle and in the pons. The cerebral cortex also showed some reaction associated particularly with small hemorrhagic lesions of the meninges. The minuter characteristics of the lesion indicate that there is a non-suppurative inflammation particularly surrounding the bloodvessels and to some degree resembling the reaction observed in poliomyelitis. Degenerative changes are also present in the nerve and glial cells. The disease has assumed epidemic prevalence in some localities in England. The causative agent is not known but it is interesting that a similar disease has previously been described following epidemics of influenza.

**The Biochemistry of *Bacillus Histolyticus*.**—In a previous paper WOLF and HARRIS investigated the problem of carbohydrate metabolism of *B. welchii* and *B. sporogenes*. In those investigations it was shown that the *B. sporogenes* was unusually active in decomposing proteins to amino acids and ammonia. Both organisms produced butyric acids and small quantities of acetic acid. These authors continued their studies upon the metabolism of anaërobic bacteria and now report the results obtained with *B. histolyticus* (*Jour. Path. and Bact.*, 1918, xxii, 1). This organism appears to be the most active destructive agent in anaërobic infections. It may be associated with other types of anaërobes which assist the activity of the *B. histolyticus*. In tissues the organism appears to melt down the muscle and soft structures denuding the bone in a process of liquefaction. These studies were undertaken upon cultures in various media. It was shown that it is essentially a protein-splitting organism attacking certain proteins with great intensity. Amino acids and ammonia are formed in the reaction along with large quantities of butyric and acetic acids. During the growth of the organism in rich protein media considerable quantities of crystalline tyrosin are formed.

**Multiple Skin Metastases from Cancer of Internal Organs.**—SUZUKI (*Jour. Cancer Res.*, 1918, iii, 357) has collected 110 cases from the literature and 5 of his own wherein metastases have arisen in the skin from internal cancers. Skin metastases are quite unusual in all forms of cancer and it is interesting that there are certain types which are prone to induce such localizations more commonly than others. In the majority of instances the primary tumor was in the stomach, intestine or uterus. They appeared slightly more commonly in the female than in the male. Curiously enough in 11 such cases reported from Japan the frequency of male to female is reversed in the proportion of 9 to 2. This the author believes is because cancer in general is more common in the male than in the female in Japan. These skin metastases are usually of the nature of adenocarcinoma and make their appearance upon the thorax and abdomen in the majority of cases. Next in frequency are the back and neck. It is not clear why this disposition upon the skin surfaces should take place. In certain regions the localization of the metastases in the skin is dependent upon a rich and neighboring lymphatic supply. The presence of skin metastases is of serious prognosis, the majority dying within three months.

**Occupational Cancer.**—For a number of years evidence has been accumulating to indicate the importance of certain factors in occupations causing a predisposition or as some would have it, producing a precancerous state whereby malignant tissue changes more readily arise. For the most part we have been willing to accept the fact that certain types of damage have a greater tendency to bring about these particular predisposing changes than others, and there is little information other than studies upon morphological changes, suggesting the underlying factors which relate these new tissue states to the development of neoplasm. H. C. ROSS (*Jour. Cancer Res.*, 1918, iii, 321) has collected the evidence in Great Britain of the occupational factors associated with new growth. He has particularly interested himself

in coal, coal-tar and its derivatives. He finds that the derivatives of different kinds of coal differ somewhat in their qualities of inducing the precancerous conditions and he finds also that the pitch of gas works is much more harmful than that obtained from the blast furnace. He points out that the factor of mechanical irritation as induced by coal is much less important than the chemical stimulus of coal derivatives. Thus he finds that the various partially refined products contain a quality which is not as evident in the original coal nor in some of the highly refined products of different chemical constitution. In this way he compares the effects of coal, tar, pitch, soot, anilin dyes and petroleum. He compares these results with those obtained in kangri burns, tobacco, beetle-nut, x-ray ulcers, etc. After reviewing the importance of these various types of semi-experimental cancer he applies his theory of auxetics advanced in 1911. The author believes that these stimulating substances or auxetics are produced in decaying organic matter and are either of endogenous or exogenous origin. Thus in chronic ulcers the decomposition of the individual's own tissues gives rise to these unknown chemical stimuli, while similar or allied bodies arise in manure and the slow decomposition of organic matter as seen in the coal deposits. With this theory based upon the properties of such indefinite and unknown substances there is much opportunity for speculation with little definite information, however, for advancing an understanding of the cancerous process.

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**A Case of Mucor Infection.**—It is quite unusual to find any of the types of mucor pathogenic to man. ERNST (*Jour. Med. Res.*, 1918, xxix, 143) reports the isolation of a *M. corymbifer* from a healthy young adult who was suspected of suffering from tuberculosis. Clinically no lesion could be demonstrated in the chest but there were a number of ulcers upon the vocal cords. The examination of the sputum was repeatedly negative for tubercle bacilli, but on several occasions the mucor was demonstrated in the stained smears and was also isolated in culture. It is suggested that the infection may have been gained from working with cereal products where this type of mould is not uncommon.

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**Studies on Uranium Poisoning.**—KARSNER and his associates (*Jour. Med. Res.*, 1918, xxix, 157) undertook a study of the poisonous effects of various uranium salts. They point out that although uranium is one of the less frequent metals met with, yet with the development of certain war industries it was being used as a substitute for tungsten in the making of alloys. Under these conditions it is possible that fair quantities of uranium may find their way in the shape of powder and dust into the respiratory and digestive tracts. It is mainly in the form of the uranium oxide that this contamination may occur. The uranium oxide in itself is insoluble in water and as such can be non-toxic. But these authors have shown that because of its solubility in hydrochloric acid the presence of uranium oxide in the stomach may lead to a sufficient solution and absorption to cause intoxication. Such was actually demonstrated in the experiment. The various salts of uranium all show poisonous effects, the action being mainly upon the kidney. The authors were able to show that the main excretion is accomplished by

way of the kidney and that the severity of the functional and anatomical disturbance is due to the concentration of the metal in this organ. The presence of uranium in the kidney is not because of a special affinity of the kidney tissue for uranium but rather the accumulation of it through the functional activity of excretion. The authors were also able to demonstrate by an experiment that a state of acute intoxication was largely one of an acid intoxication following upon the kidney lesion. They indicate that the amount of acid intoxication is in proportion to the kidney lesion and that the kidney disturbance precedes the evidence of decreased alkali reserve in the blood.

**Brom Cresyl Purple and Litmus as Indicators for the Classification of Tubercle Bacilli.**—It is desired in bacteriology to devise a technic which will indicate the biological activity of microorganisms during the period when they are under observation. Not a few cultural methods are in practice for this purpose. Many tests are used for demonstration of the production of acid by particular organisms from various materials. The usual methods in use do not indicate quantitatively the production of these acids. The H-ion concentration can, of course, be determined in the cultural media at any particular period but the method becomes cumbersome if it is to be applied repeatedly to the same culture or to many different observations during a given study. It is to be found that there are certain indicators which by a color reaction give a fairly wide range of color display in different reactions of the medium. Some of these indicators differentiate both the grades of alkalinity as well as acidity. With this in mind FROTHINGHAM (*Jour. Med. Res.*, 1918, xxix, 153) has studied the variation in the color display of two indicators with particular reference to the reactions taking place in cultures of tubercle bacilli. Theobald Smith has by titration methods shown that the human strain of tubercle bacilli when growing in a glycerine broth tends to cause a primary alkaline reaction followed by an acid production, while the bovine type produces a primary alkalinity which is not followed by acid production although the amount of alkalinity after weeks of time is somewhat diminished. The presence of brom cresyl purple in the culture demonstrated fairly well the development of alkalinity by a purple color and a light lemon-yellow color when acid appeared. All gradations between these two colors lay between the distant extremes. With the use of litmus a somewhat similar but less satisfactory result was obtained. The author points out that by a careful study of such color reagents and with a definite knowledge of the meaning in terms of the H-ion concentration of definite shades of color much use may be obtained by the application of these indicators.

**A Study of Experimental Organizing Pneumonia.**—Recent years have demonstrated that there is much still to be learned respecting pneumonia. This is true not only of its epidemiology, bacteriology, but also of its pathology. We are realizing more than formerly that the types of inflammatory reactions within the lung are dependent upon definite factors which may be determined and that the vagaries so often noted are not merely the chance development of peculiar reactions. Best known to us is the sequence of events in lobar pneumonia of pneumococcus origin. When, however, any differences occur from the usual



train of pathological events we are still largely at sea in appreciating fully what has taken place. One of these unusual events is the occasional organization taking the place of the more common complete resolution. For some reason the lung parenchyma responds to an irritant in a manner not unusually observed in pneumococcus pneumonia. WADSWORTH (*Jour. Med. Res.*, 1918, xxix, 147) undertook an experimental research attempting to reproduce the condition found in the human. He made use of dogs, using the Meltzer method for the production of pneumonia. A number of animals were infected with the pneumococcus. None of these showed evidence of organization. Another series of animals was infected with the *Staphylococcus aureus*. These animals developed bronchopneumonic lesions in which resolution was delayed and the beginning of abscess formation observed. The third series of animals received a mixture of pneumococcus and staphylococcus. By these means it was hoped to obtain more extensive lobar lesions by the pneumococcus which might favor the activity of the staphylococcus with delayed resolution and organization. Difficulty was experienced in gauging the proper dosage and many of the experiments were negative. Two animals, however, killed on the fifteenth and nineteenth day, showed irregular areas of consolidation around the bronchi, partly acute and partly unresolved with early organization. The experiments indicate that the pneumococcus will give rise to unresolved pneumonia with organization only in the presence of a complicating or secondary infection. It is possible that with certain organisms constituting the secondary infection a symbiosis with the pneumococcus is necessary to permit them inducing the proper grade of reaction whereby organization results. It is of course also to be remembered that there may be other bacteria acting in pure culture which may produce types of organizing pneumonia, as has been suggested by MacCallum and Cole, as for instance the pulmonary streptococcus infection following measles.

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## HYGIENE AND PUBLIC HEALTH

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**Safe Limit of Carbon Dioxide in the Working Atmosphere.**—HIGLEY (*Am. Jour. Public Health*, July, 1918) states that in the opinion of Flügge one may breathe for several hours air containing twenty times the usual permissible percentage of carbon dioxide without perceptible deleterious influence upon his health. The more rigorous methods of the New York State Commission for Ventilation reveal

the fact that stagnant air containing two to fifteen times the generally accepted amount of carbon dioxide may be respired seven hours per day for five or more weeks with no perceptible effect upon heart-rate, on increase of heart-rate on standing, on blood-pressure, Crampton value or respiration of the subject. On the other hand, all the deleterious effects that were formerly attributed to respiring carbon dioxide present in the stagnant air may be produced by breathing, for the same period, air that is practically free from carbon dioxide but which has a temperature of say 90° F. and a very high relative humidity. Also that a cold, dry air when heated to 80° or more without humidification may produce, when respired for some time, the deleterious results so beautifully demonstrated by Cocks. The matter is well summed up by Professor Lee when he says that "the problem of ventilation is physical rather than chemical, cutaneous rather than respiratory." In view of the fact that recent investigations have apparently shown carbon dioxide to be harmless when respired in much larger amounts than 0.08 per cent., the writer suggests that the safe limit of this gas in the working atmosphere be placed at 0.2 per cent.

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**Sterilization of Woollen Blankets and Uniforms.**—FULTON and STANIFORD (*Jour. Am. Med. Assn.*, September 7, 1918, p. 823) state that the following procedures effectively sterilize woollen goods without deterioration or shrinkage: Woollen blankets or uniforms are placed on hangers or loosely on the trays in the sterilizer. Sixty pounds of steam is introduced into the outer jacket of the sterilizer to prevent subsequent condensation of steam within the sterilizing chamber. A vacuum of from fifteen to twenty inches is created in the sterilizer chamber to facilitate penetration of the clothing by steam. Sterilization is performed with either 0 pounds of steam for one hour, designated as the atmospheric pressure method, or 12 pounds of steam for ten minutes, designated as the pressure method. Again a vacuum of from fifteen to twenty inches is produced to facilitate drying. The door of the sterilizer is opened about four inches for ten minutes to allow gradual cooling of the contents of the sterilizer.

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**Studies in Bovine Mastitis. II. The Relation of Hemolytic Streptococci to Udder Infections.**—JONES (*Jour. Exper. Med.*, September 1, 1918) states that hemolytic streptococci produce more or less severe inflammations of the udders of cows. Frequently infected quarters are swollen, firm, hot and tender. In a number of instances it has not been possible to detect gross changes in the mammary gland. While invasion of the udder with hemolytic streptococci has not been observed so frequently as infections with non-hemolytic types, nevertheless serious losses occur from these infections. Of nineteen cows under observation for an extended period, only four recovered. The udder may become invaded at any time during the lactation period. Doubtless the principal method of entrance is through the teat canal. Injuries play only a minor part as a predisposing factor. Animals suffering from mastitis in one quarter associated with hemolytic streptococci frequently shed identical streptococci in the milk from other quarters. Often the organisms are in pure culture or make up the bulk of the flora of that quarter. These invasions rarely produce gross changes in the gland

and frequently fail to change the character of the milk. Cows affected in this way are of considerable danger to other animals in the herd. The milker is usually warned of the infectious nature of the secretions of the diseased quarter, but may be careless in handling milk from apparently normal quarters. This may explain one ready source of infection. The pathogenicity of hemolytic streptococci obtained from cases of mastitis to species other than bovines is undetermined. Raw milk from large dairies must contain a considerable number of these organisms. Usually only the milk from clinically affected quarters is discarded, but the secretion from the other quarters not visibly involved which often contains large numbers of streptococci enters the milk supply. If any considerable number of these organisms were pathogenic for consumers of milk, septic sore-throat would occur with considerable frequency; nevertheless, milk containing a few flocculi and hemolytic streptococci obtained from cows which fail to show gross lesions must be looked upon with suspicion until more is known of the source and nature of the virus.

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**Attempts to Induce Poliomyelitis in Small Laboratory Animals.**—STIMSON (*Hygienic Laboratory Bulletin*, No. 111, p. 31) states that no evidence was adduced by his experiments to show that rabbits, guinea-pigs or rats are susceptible to poliomyelitis. Other observers have reported the successful infection of rabbits and guinea-pigs with poliomyelitis virus. Their methods did not differ essentially from those employed by Stimson. The discrepancy, therefore, must be attributed to one or the other of two causes, according to Stimson: either the strain or virus employed by these observers differs from his in its pathogenic properties or it is contaminated with some organism capable of producing these symptoms in small animals.

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**Epidemiological Studies of Poliomyelitis in New York City and the Northeastern United States During the Year 1916.**—LAVINDER, FREEMAN and FROST (*Public Health Bulletin* No. 91, July, 1918) state that poliomyelitis is, in nature, exclusively a human infection, transmitted from person to person without the necessary intervention of a lower animal or insect host, the precise mechanism of transmission and avenues of infection being undetermined. The infection is far more prevalent than is apparent from the incidence of clinically recognized cases, since a large majority of persons infected become "carriers" without clinical manifestations. It is probable that during an epidemic such as that in New York City a very considerable proportion of the population become infected, adults as well as children. The most important agencies in disseminating the infection are the unrecognized carriers and perhaps mild abortive cases ordinarily escaping recognition. It is fairly certain that the frank, paralytic cases are a relatively minor factor in the spread of infection. An epidemic of one to three recognized cases per thousand, or even less, immunizes the general population to such an extent that the epidemic declines spontaneously, due to the exhaustion or thinning out of infectable material. Apparently an epidemic incidence relatively small in comparison to that prevailing in an epidemic may produce a population immunity sufficient to definitely limit the incidence rate in a subsequent epidemic. It is, of course,

to be expected that further experimental and epidemiological research will modify this view and will more fully explain all the phenomena of this disease. It may, however, be noted that other more common infectious diseases, generally considered "familiar," present problems as little explained as those of poliomyelitis and that broader studies of these diseases may be expected to assist in interpreting some of the facts established regarding poliomyelitis.

**A Clinical Study of the Frequency of Lead, Turpentine and Benzine Poisoning in Four Hundred Painters.**—HARRIS (*Arch. Int. Med.*, August, 1918, xxii, 129-156) undertook this study to obtain a more concise idea of the extent to which actively employed workers, most of whom thought themselves in excellent health, gave evidences of damage inflicted by lead paints. One hundred and sixty-three, a rate of prevalence of 40 per cent., of active cases of lead poisoning were found among the 402 painters examined. All of these showed definite clinical signs of plumbism; 72, or 44 per cent., of the active cases of lead poisoning among these painters were found to have lead in the urine in addition to clinical evidence. Thirty-five, or 8.7 per cent., of the total number were found to have lead in their urine without manifest clinical signs. In other words, nearly one-half of all the painters examined, or 48.7 per cent., gave evidence of active or latent lead poisoning. No attempt was made to distinguish between the effects of turpentine, benzine, wood alcohol, acetone, benzol, etc. At least 70 per cent. of all those examined gave a fairly clear and recognizable history of at least one or many attacks, and 142 painters gave a history of recent severe intoxication, in which several or even all of the following symptoms were noted: a sudden sense of weakness in the legs, irritation of the eyes, difficulty in breathing and dryness and irritation of the throat, cough, headache and dizziness, which in a number of cases was so pronounced that frequently a history of falls from scaffolding or ladders was obtained. In addition, there were often present nausea, vomiting, painful and frequent urination during the day, a few cases of bloody diarrhea, and several others of bloody urine. Practically 60 per cent. of the recent cases of turpentine and the related type of intoxications were found among our 163 active and 35 latent lead-poisoning cases out of the total of 402. Forty-seven of the 142 recent cases had suffered from frequent and moderately painful urination. Occasionally, symptoms that indicated strangury with bloody urine were described. Twenty-three of this group complained of frequent attacks of vertigo. A comparatively small number survive as active members of the trade after having attained the age of fifty years. Also, 64 per cent. of the active cases of lead poisoning occurred between the ages of thirty and forty-nine years, whereas 71, or 45 per cent., of all those who apparently were free from symptoms of plumbism were less than thirty years of age. Taken in connection with the fact that most painters enter the trade before their twentieth year, and, being skilled workers, follow it the rest of their lives, and, furthermore, that of the 109 who were more than forty years of age 59 per cent. were found to be suffering from active or latent plumbism, it seems fair to conclude that the action of lead is slow in asserting itself, but that less than half who have passed the age of forty years escape the disease. The remedial measures

that suggest themselves may be divided into two general classes: (1) public health measures, contained in better sanitary conditions for the workers, (2) and instruction in personal hygiene as applicable to the trade.

**The Virulence of the Tubercle Bacilli Isolated from the Sputum.**—CORPER (*Jour. Infect. Dis.*, December, 1918, No. 6, xxiii, 493) states that it is rather singular that the tubercle bacillus was one of the first pathogenic microorganisms isolated in pure culture, and yet its virulence in the sputum, the most important route of exit from the body in man, has been studied only in an unsatisfactory manner considered from a hygienic and sanitary standpoint. He isolated tubercle bacilli by Petroff's method from the sputum of 90 cases of pulmonary tuberculosis in man, of which 8 were incipient, 20 moderately advanced and 62 far advanced. The bacilli in 88 of these cases were of the human variety. Of these 88 cultures examined for virulence to guinea-pig (by subcutaneous injection), 86 proved to be virulent in amounts of 0.000,001 mg., 10 of these were not examined below this amount and 66 produced tuberculosis (beyond the local glands) in guinea-pigs within two months in 0.000,000,01 mg. amounts. One of the two low virulent tubercle bacilli only produced a slight tuberculosis in guinea-pigs in 0.001 mg. amounts within two months, while the other produced no tuberculosis beyond the local involvement even in 1 mg. amounts. No relation was observed between the virulence of the human tubercle bacilli for the guinea-pigs and rabbits and the rapidity of the disease in man. No appreciable difference, within the limits of error of the experiments, between the virulence of human tubercle bacilli tested by subcutaneous injection for young (four months) and mature (one year) male guinea-pigs was noted sixty-two days after infection. Human tubercle bacilli isolated on Petroff's medium do not appreciably alter their virulence for a period of one to three months as tested in guinea-pigs, provided no detrimental influences are introduced. A second seeding on Petroff's medium within this time produces bacilli of equal virulence to guinea-pigs to the primary. Treatment of human tubercle bacilli with 3 per cent. NaOH solution for one hour at 37° C. does not appreciably affect the virulence of the bacilli for guinea-pigs, while 6 per cent. NaOH for one hour at 37° C. will destroy the virulence of some cultures. The test for virulence of human tubercle bacilli isolated from the sputum of the same patient at different intervals (one and three months) gives concordant results in guinea-pigs.

**Botulism.**—DICKSON (*Arch. Int. Med.*, October, 1918, xxii, 483-495) concludes from his studies that the use of home-canned foods is not wholly unattended with danger. Various methods of canning were adopted and were followed as carefully as it is possible to have untrained persons conduct technical procedures. He states that the fact that in several instances the greater part of the home-canned material remained in good condition simply proves that though the methods are efficient in preventing ordinary spoilage, they are inefficient if the raw material happens to be contaminated with spores of *B. botulinus*. It is essential that only freshly picked raw material should be used for canning and it should be blanched before it is placed in jars. One outbreak showed

clearly that three hours' sterilization in the washboiler was not sufficient to kill spores of *B. botulinus* in vegetables which had been freshly picked and had been boiled for twenty minutes in an open kettle before being packed into 1-pint jars, a procedure which should be at least as efficient as simple blanching. Dickson further states that it is unsafe to eat or even taste home-canned products before they have been boiled. It is well known that the toxin of *B. botulinus* is quickly destroyed by heat. It is of the utmost importance that those who are directing the home-canning industry should recognize that the present methods of home-canning are not entirely safe, especially in the hands of untrained workers. If they will but admit this fact and will instruct the public that there is possible danger of poisoning from home-canned products, and that the danger may be averted if all home-canned food is boiled before it is eaten or even tasted, outbreaks of botulism from home-canned products will entirely cease.

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**Reliability of Ozone in Swimming Pool Disinfection.**—MANHEIMER (*Jour. Am. Med. Assn.*, June 29, 1918, lxx, 1991-1992) recommends ozone for swimming pool purification for the following reasons: (1) It is reliable as a disinfectant; (2) it is capable of purifying heavily polluted pool water; (3) it produces no objectionable substances in the water; (4) it improves the appearance and transparency of the water, permitting a longer continued use of the pool, a consequent reduction in the cost of maintenance, and a reduction in the hazard of drowning; (5) it is inexpensive in application.

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**Experimental Scurvy of Guinea-pig in Relation to Diet.**—COHEN and MENDEL (*Jour. Biol. Chem.*, September, 1918, xxxv, No. 3) state that experimental scurvy of guinea-pig may be demonstrated at will with suitably chosen diets. Exclusive diets of cereal grains like oats and barley produce the disease. Germinated oats or barley prevent the appearance of scurvy even when fed for comparatively long periods. Scurvy arises on a diet of soy-bean flour, even when the latter is supplemented with fat soluble and water soluble vitamins, inorganic salts and cellulose. Small additions of raw milk do not prevent the onset of scurvy. Larger quantities cause the symptoms to disappear. Roughage in the diet plays, if anything, a minor accessory role in the prevention of scurvy. This disease is not essentially dependent on constipation as a causative factor, though the latter may aggravate the symptoms. Cabbage seems to retain some antiscorbutic properties even when dried. Contrary to current statements, highly purified lactose, fed with a scurvy-producing diet appears to have no effect on the course of the disease.

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CLARENCE JOHN BLAKE, M.D.



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## CLARENCE JOHN BLAKE, M.D.

I HAVE been asked to write a few lines about the late Clarence John Blake, M.D., of Boston, Massachusetts. I shall not attempt to enumerate the offices which he held, the names of the societies of which he was a member or the papers which he wrote upon medical or other subjects. For all of these things I must refer to the records, which are compiled and kept for reference, concerning the lives of prominent men.

My endeavor will be to convey the impression which certain of Dr. Blake's characteristics made upon me during a fairly intimate professional companionship covering some twenty odd years.

First and foremost, I wish to speak of his great and unfailing kindness to his patients, whether hospital or private. Their welfare and relief were the *only* things which he thought about. No time (whether night or day) and no trouble or inconvenience were ever allowed to weigh for a moment against a possible benefit to the patient, and he gave himself absolutely, both brain and body, to their service. Thousands of his patients are today lamenting his loss, not only because they have lost a skilled physician who helped their ailments, but because they feel that they have also lost a friend who took an intense interest in all that affected them and to whom they could go for advice and counsel on any subject, whether medical or non-medical, with the certainty that he would give both time and thought to an endeavor to help them. This was a marked characteristic of Dr. Blake, and I wish to lay great stress upon it.

His intelligence was very keen, his mind very active. He saw more, and more quickly, than other men, and what he saw suggested all sorts of possibilities to him, of which he was very quick to make use. This was a great help to him in original investigation.

It so happened that Dr. Blake was among the first in this country who made a specialty of otology after the invention of the forehead mirror had revolutionized that branch of medicine by allowing the doctor to see into the ear. He therefore belongs to those who *created* the treatment for aural diseases, and he took advantage of his great opportunities and did his full share toward the rapid advances which were then made. He studied for a long time under Prof. Politzer, in Vienna, and was selected by him

to be his assistant, a great honor, which showed how highly he was esteemed by Prof. Politzer; and he had a very enviable international reputation during his whole life, so that when his pupils went to Europe in after years the first question asked, as soon as it was known that they came from the Harvard Medical School, was: "How is Dr. Blake? What is he doing? Is there anything new scientifically from him?"

He was loth to cause pain and was exceedingly deft and skilful with his fingers, and he taught all who came under his tutelage how to perform all the painful and unpleasant things which an aurist has to do, with a minimum of pain and distress to the patient. This also I wish to lay stress upon, although it is a small thing, for it saved the patient from untold misery.

I first knew Dr. Blake when I applied as a volunteer during his service at the Massachusetts Charitable Eye and Ear Infirmary, and he was kindness itself in explaining and showing me all that pertained to the anatomy of the ear and nose and to the diagnosis and treatment of their diseases. He was a wonderful and most interesting teacher, and no assistant or house officer has ever worked with him or under him without learning more from him than he could ever have learned from all the text-books in creation. I can freely say that he taught me the most of what I know about otology, although I often did not agree with him as to treatment. I knew him first as an assistant, then as a colleague, and for years he used to send certain cases to me for treatment, and we consulted together about them. If I was worried about a serious and dangerous case I always went to him for advice, and I have never done so, whether in the middle of the night or at meal times, or after his long office hours were over, that he did not give his best thought to the case; and if it seemed necessary he would go at once (whether by night or day) to see the case with me. He never failed me, and was never too tired to help a patient who was in pain or danger.

Dr. Blake and I differed many times and about many things, but my respect for his unfailing kindness, his quick perceptions and his alert and resourceful mind was very great, and he certainly did a great deal for both the scientific and the practical side of otology.

HENRY LEE MORSE, M.D.

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ORIGINAL ARTICLES

**ROENTGEN-RAY INTOXICATION: DISTURBANCES IN METABOLISM PRODUCED BY DEEP MASSIVE DOSES OF THE HARD ROENTGEN RAYS.**

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AND

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THIS paper deals with the general constitutional reaction which follows prolonged exposures to the roentgen rays of the Coolidge tube. The experiments tabulated below give data to show the increase in nitrogen elimination and in blood non-protein nitrogen which precedes the fatal intoxication. Some of the interest centers upon the intestinal epithelium which gives evidence of injury, and it is possible that this injured epithelium may be responsible in large measure for the clinical symptoms of vomiting, diarrhea and prostration. The parenchymatous organs, with the exception of the spleen, give no evidence of any specific injurious action of the roentgen rays. We can submit no evidence for any specific action of the roentgen rays upon cell ferments, but the remarkable specific action of the roentgen rays upon certain cells speaks for an individual peculiarity of these cells apart from their autolytic ferments. It may be that the cell ferments are wholly responsible for the cell autolysis and disappearance once the primary specific cell injury has been effected by the roentgen rays.

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We became interested in this subject following a study of roentgen-ray burns. The long latent period of the roentgen-ray burn and the lack of systemic reaction have never been satisfactorily explained, nor can we bring any sufficient explanation at this time. Much more is known about the intoxication of the common heat burn, and the evidence is pretty conclusive that body protein in the burned area is injured in such a manner that toxic split products are formed and absorbed into the body. If these toxic protein split products are in sufficient amount there will result a fatal systemic intoxication.

That roentgen rays were capable of producing burns was noted very soon after their discovery, probably first reported by Leppin.<sup>11</sup> Since that time the records have multiplied into the hundreds. The late results of roentgen-ray burns and irritations which may result in cancer growth began to appear. Soon it was pointed out by Albers-Schönberg<sup>1</sup> and Halberstaedter<sup>18</sup> that sterilization could be effected by the roentgen rays, and must be guarded against.

*Constitutional reactions* following the roentgen-ray treatment began to be noted. Perhaps the first on record is that reported by Walsh.<sup>56</sup> The danger of these systemic reactions has been repeatedly emphasized by Edsall and his collaborators.<sup>12 14 15</sup>

It is safe to state that the frequency of these constitutional reactions is on the increase, and we wish to point out the danger of such reactions. The Coolidge tube is mainly responsible for this because by means of the improved tube it is now possible to administer "massive" doses (Cole<sup>8 9</sup>) to structures below the skin and by "cross-fire" escape the danger of a burn. The "hard rays" of a Coolidge tube with a wide spark gap have much greater capacity to cause the tissue injury which is responsible for the constitutional reaction than had the older tubes. (Note Table XV.)

The general systemic or constitutional reaction varies considerably as reported by various writers who have observed these reactions in their patients following roentgen-ray treatment. There is much variation as regards the dosage of the roentgen rays, filters used, spark gap, etc. The reaction may begin shortly after the irradiation or be delayed for days. As usually described it consists of loss of appetite, malaise, nausea and vomiting. Diarrhea may be severe and prostration may be profound. Some authors record slight fever and others a slow, weak pulse, with subnormal temperature. In the University of California Hospital not long ago two boys were treated for ringworm of the scalp, and their mother reported that after going home they became very sick and vomited for several hours.

The general constitutional reaction which follows the use of large doses of the roentgen rays is of considerable interest because of a certain resemblance to intoxications in dogs caused by proteose injections. Both may be regarded as true "non-specific" reactions

associated with much destruction of body protein and these intoxications are to be compared with other "non-specific" intoxications: for example, intestinal obstruction and acute pancreatitis. Therefore a study of the intoxication due to treatment by the roentgen rays takes on a new interest because it is one of the "non-specific" intoxications. Bacteria and specific toxins and endotoxins or antibodies cannot possibly be concerned. It is practically sure that all specific infections and intoxications are associated with a certain unknown "non-specific" factor of disease, a proper understanding of which may be obtained by careful study of all types of pure "non-specific" intoxication. The roentgen-ray intoxication is an important member of this group of pure "non-specific" intoxications.

Many papers deal with this constitutional reaction: Edsall and Pemberton,<sup>14 15</sup> Lange<sup>20</sup> and Pfahler.<sup>42</sup> Pfahler believes that the symptoms are due to poor ventilation of the roentgen-ray room, causing the patient to inhale certain gases produced in the air by the action of the high-tension current. In a slightly different form this theory was also advanced by Wilbert,<sup>59</sup> although the two authors differ as to the exact nature of the noxious gases produced. This argument may be dismissed without comment.

Lange maintains that the reaction is the result of an acidosis resulting from cellular degeneration or from increase in catabolic cellular activity. He submits no analyses of blood or expired air to support this claim. On this theory he attempts to counteract the constitutional effects with doses of sodium bicarbonate.

Edsall and Pemberton advanced a theory which we believe to be more nearly correct. They noted that roentgen rays sometimes produced a constitutional reaction which they ascribed to an acute intoxication. They state, as their belief: "The tissue destruction accomplished by roentgen rays undoubtedly involves chiefly tissues especially rich in nucleoprotein. The decomposition products of this form of protein are especially rich in substances that are more or less toxic and difficult to metabolize and excrete." Further: "The intoxication is not dependent directly upon alterations in the excreting power of the kidneys because examinations of the urine of two patients showed no evidence of irritation of the kidneys. It is, however, probable in many cases, after a time, that the kidneys do become overtaxed by the added labor thrown upon them and their excretory power fails to a greater or less degree, and this may increase the toxic symptoms."

The source of these toxic products and the mechanism by which the roentgen rays produce their physiological action still remain subjects of dispute. As to the former, several theories have been advanced.

1. It has been claimed by Linser and Sick,<sup>34</sup> Engel<sup>16</sup> and others that the roentgen rays produce a roentgen toxin in the blood which might be responsible for the increased protein destruction. As

might be expected, it is impossible to demonstrate any such roentgen toxin in the blood, and the experiments submitted are not controlled. Many toxic substances introduced into the blood are removed so rapidly as to defy detection, so a negative result gives no assurance that a powerful toxin may not have been present in the blood.

2. It has been claimed by Heile<sup>19</sup> and others that the destruction of the white blood cells resulted in the release of a great store of powerful intracellular enzymes, which then attacked various tissues to produce the protein degradation noted. But we now know of powerful anti-enzymes which are constantly present in the blood during life.

3. It has been suggested by Baerman and Linser,<sup>2</sup> Rosenstern,<sup>51</sup> Edsall<sup>12</sup> and others that roentgen rays may have a stimulating effect on enzyme activity in general and particularly in these cases on the enzymes which produce tissue autolysis. Edsall, acting on this hypothesis, concluded that roentgen rays might be of value in the treatment of unresolved pneumonia. He used them in a number of such cases and reports excellent results—Edsall and Pemberton.<sup>14</sup>

Much work has been reported on the effect of roentgen radiation on ferment activity, and this might be cited to substantiate the last-mentioned theory. There is also a relatively large literature on the effect on enzymes produced by radium emanations, and it is now generally accepted that the two kinds of radiant energy are practically identical in their physiological action. Wohlgemuth<sup>60</sup> showed that radium rays stimulate the autolysis of tuberculous lung tissue *in vitro*. Neuberg<sup>40</sup> demonstrated that fresh carcinoma tissue autolyzes more rapidly *in vitro* under the influence of radium emanation than does a control not so exposed or similar tissue which had first been cooked before being rayed. He also makes the statement that radium inactivates trypsin, rennin, pepsin, etc., and believes that this furnishes a key to its action on cancer tissue; that it causes destruction of all intracellular ferments which bring about anabolic processes, while those producing autolysis are unaffected. In modern terminology he believes radium acts by destruction of anti-enzymes.

The best work on the effect of roentgen rays on ferments is that of Richards,<sup>46</sup> in which he demonstrates that a short radiation with roentgen rays accelerates enzymatic activity while a longer radiation inhibits it. This holds for the digestion of egg albumen by pepsin and of starch by diastase. "Between these two strengths," he says, "lies a point at which the radiation is non-effective." He does not believe, however, that the effects of radiation on enzymes, which he has demonstrated, are sufficient to account completely for its action on cells. On the other hand, Richter and Gerhartz<sup>47</sup> maintain that the effects noted by other authors—at times an increase, at others a decrease in ferment activity—are due to experimental errors. They claim that roentgen rays have absolutely no

effect on ferments and that theories which attempt to explain the biological action of roentgen rays through the influencing of enzymatic processes, "auf sehr schwachen füssen stehen." A very interesting review of this whole field is given by Richards.<sup>46</sup>

One other feature seems worthy of attention as the attempt has been made to charge the constitutional effects following prolonged exposure to roentgen rays to the production of a nephritis. That roentgen rays produce a nephritis has been claimed by many workers—Linser and Helber,<sup>33</sup> Rosenstern,<sup>51</sup> Warthin<sup>52</sup> and others. On the other hand, negative findings are reported by Buschke and Schmidt,<sup>7</sup> Krause and Ziegler<sup>28</sup> and others, and several of those who have reported positively admit that the renal trouble is very transitory. Careful examination of the kidneys of our series of animals at autopsy and of the microscopic sections has convinced us that if there is renal injury it is of a relatively slight grade and is not a constant finding. Indeed, the fact that its existence is under dispute demonstrates that it must be of a very slight grade. Perhaps we may assume that the renal epithelium like other body cells may be injured by the roentgen rays, but this injury cannot be extensive because function is but little disturbed and the anatomical changes when present are admittedly slight.

Numerous contributions are to be found in medical literature dealing with metabolism studies of persons treated by the roentgen rays or by radium. Almost all of these reports deal with patients suffering from acute or chronic leukemia. For a review of this literature we wish to refer to the excellent papers of Keymling<sup>25</sup> and Murphy and Means and Aub.<sup>38</sup> It is best to summarize some of the outstanding facts which we must keep in mind during the discussion of the experiments given below.

Leukemic patients show an increase in basal metabolism and usually a negative nitrogen balance. The uric acid of the blood is usually above normal and the endogenous uric-acid elimination usually increased. There may be retention of phosphates. The changes are more striking in acute leukemia and may be quite variable in chronic leukemia.

Treatment with the roentgen rays may not have any definite effect on leukemia cases (Goodall<sup>17</sup>), but usually causes an increased elimination of nitrogen, uric acid and purin bases. The fall in the leukocyte curve does not bear any constant relationship to the elimination of nitrogenous substances.

Most of the work done with the roentgen rays concerned abnormal human beings: leukemia, Hodgkin's disease and the like, but some work has been done upon normal animals and human beings.

Quadrone<sup>44</sup> studied one guinea-pig and six rabbits. His results were not uniform, but in most cases he got a slight increase in the  $P_2O_5$  output following radiation. Bloch<sup>5</sup> studied the metabolism of one man rayed for chronic eczema. He found that the rays caused

increased uric-acid output in the urine, also an increased output in the  $P_2O_5$  and purin bases. Benjamin and v. Reuss<sup>3</sup> rayed one dog and studied his metabolism. Their animal developed constitutional symptoms similar to those of our series and showed an increase in N elimination beginning immediately and lasting several days, transient increase in  $P_2O_5$  output and very transient appearance of cholin in the blood. Lommel<sup>25</sup> conducted metabolism observations on three young dogs with similar results, and Linser and Sick<sup>24</sup> studied five human patients under roentgen treatment for various skin diseases. None of their patients became sick but all showed an increase in urinary N of 2 or 3 grams while their uric-acid output tripled in some cases, and the purin bases also increased. They repeated the experiment on one normal dog, with similar results.

#### METHOD.

Dogs were used in all experiments, and unless otherwise noted in the charts were in normal condition. The dogs were usually starved for two or three days before the urinary collections were initiated. Dogs were kept at all times in large metabolism cages constructed with sharply pitched floors to facilitate the complete collection of urine. All fluids were given by stomach tube unless the dog was vomiting constantly, when the fluids were placed in a cup fixed in the cage. In such experiments the nitrogen analysis includes the vomitus, but it is known from many analyses that such vomitus contains only a trace of nitrogen. Every day at the same hour the dog was catheterized, the urinary bladder rinsed out and the fluids given by stomach tube, the cage washed and all cage urine measured. The cage urine, cage washings and catheter specimens were combined, diluted to a unit volume and duplicate analysis of samples for nitrogen made by the Kjeldahl method.

When the dog had reached a level of nitrogen elimination under these conditions the animal was given morphin, to prevent restlessness, followed by the roentgen-ray treatment. The Coolidge tube was used in all cases and the distance of the anticathode from the dog's body was in all cases ten inches. The roentgen-ray dose was given on each side of the abdomen and on each side of the thorax, one-fourth of the total dose on each area. Some preliminary work was necessary to determine the roentgen-ray dose necessary to produce skin injury or a constitutional reaction. It was soon found that the thick hairy dog's skin was very much more resistant than the human skin. It is probable that the dog is more resistant to the constitutional effect of the roentgen rays but the data available is scanty. Observations are usually recorded on diseased and abnormal human beings, and there is usually no record of the spark gap, which we shall see is an important factor. Aluminum filters (2 mm.) were usually used unless otherwise noted for the systemic reaction, but not used when a dermatitis was desired.



## EXPERIMENTAL OBSERVATIONS.

The first two experiments given below (Tables I and II) show the result of a fatal dose of the roentgen rays. The first dog was given a very large dose (500 ma. minutes), probably over two lethal doses as contrasted with the second dog (Table II), which was given only 200 ma. minutes—just about the minimum lethal dose. Table V shows an experiment in which a dose of 200 ma. minutes was not fatal and only caused a minimal clinical reaction. It is noteworthy that death occurred in both these experiments (Tables I and II) on the fourth day whether the dose was large or small. In the first experiment with the larger dose the nitrogen elimination is greater and the clinical reaction was more prompt, but, as a rule, the fourth day brings the maximum intoxication, followed by death or recovery. Exceptions to this will be discussed later.

Delay in the onset of clinical symptoms is well illustrated by Table II. This dog for two days was perfectly normal so far as any clinical signs could show—active and vigorous, with no gastro-intestinal symptoms. Vomiting and diarrhea appeared on the third day in spite of the fact that the dog received only water by the stomach tube. Prostration and intoxication were striking on the fourth day, and it is certain that the dog would have died late on the fourth day. This peculiar latent period must be explained by any hypothesis which may be advanced to solve the puzzle of roentgen-ray intoxication.

Autopsy findings are mainly negative. One notes that the spleen is usually smaller than normal and the lymphocytes are less numerous than normal. The heart, lungs, pancreas and liver are negative. The kidneys may show a little cloudy swelling and perhaps a few casts. The gastro-intestinal tract usually shows more or less engorgement of its capillaries and a congested mottled mucous membrane. This congestion is least in the stomach and usually most intense in the duodenum and jejunum. At times it may be most intense in the colon and ileum. There are no ulcers, but some signs of epithelial necrosis. This capillary engorgement must explain the blood-tinged diarrhea which is such a constant feature of the fatal intoxication in dogs.

TABLE I.—18-45—ROENTGEN RAY, LETHAL DOSE.

Date.	Weight, pounds.	Urine, c.c.	Nitrogen, grams.	Diet.	Remarks.
Oct. 1	23.93	460	2.38	400 c.c. water	Dog normal; slight cystitis.
2	23.37	520	2.52	400 "	
3	23.00	440	....	400 "	
3	Roentgen ray—500 ma. min., 2 mm. aluminum filters, spark gap 9 ins.				
4	22.00	545	4.20	400 c.c. water	Dog dull.
5	21.81	550	5.88	400 "	Vomiting.
6	20.62	410	7.34	400 "	Dog very sick; vomitus;
					blood N. P. N. = 50 mg.
7	Dead	655	4.76	....	Much bloody diarrhea.

*Autopsy* (Dog 18-45, Table I). Serous surfaces dry. Blood clots soft and dark red. Heart, lungs, spleen, liver, kidneys, pancreas are all normal. Bladder and urethra show a diffuse inflammation of the mucosa. The gastro-intestinal tract throughout shows congestion and a peculiar mottled appearance conspicuous in the small intestine, which is tightly constricted. There are no ulcers of any description. The mucous membrane of the stomach and intestine is velvety and engorged.

*Microscopic Sections.* Pancreas, kidney and liver show nothing but moderate capillary engorgement. Spleen is not decreased in size, its Malpighian bodies are well preserved and the pulp is engorged. Mucosa of the intestinal tract unfortunately shows much portmortem change, but it is evident that an unusual change has taken place in the epithelium covering the villi and lining the crypts. This epithelium has almost completely disappeared by autolysis, leaving empty crypts. There is but little leukocytic or inflammatory reaction, so it is probable that this autolysis happened after death, but we cannot attribute this change to the usual postmortem autolysis which begins in the tips of the villi and spreads downward involving all structures. This autolysis involves the epithelial cells of the mucous membrane and is to be referred perhaps to the peculiar effect of the roentgen rays. It is known that roentgen-ray exposure of cancer epithelium causes great increase in its speed of autolysis *in vitro*. It is of some interest that the pancreatic cells which are rich in ferments are but very little changed in this case.

TABLE II.—18-69—ROENTGEN RAY, LETHAL DOSE.

Date.	Weight, pounds.	Urine, c.c.	Nitrogen, grams.	Diet.	Remarks.
Nov. 25	21.75	455	2.69	400 c.c. water	Dog normal.
26	21.19	383	2.24	400 "	
27	20.87	351	1.74	400 "	Blood N. P. N. = 31 mg.
28	20.43	271	1.60	400 "	
28	Roentgen ray—200 ma. min., 2 mm. alumi			num filter, spark gap 9 inches.	
29	20.13	352	2.69	400 c.c. water	Dog normal.
30	19.87	402	2.41	200 = "	Dog normal.
Dec. 1	19.50	501	2.52	200 = "	Vomitus; diarrhea; dog active.
2	18.31	1025	2.97	200 = "	Dog sick; vomitus; diarrhea.
2		Sacrifice—Blood	non-protein nitrogen		= 59 mg.

*Autopsy* (Dog 18-69, Table II). Thorax, heart, lungs, thymus normal. Liver, kidneys, pancreas moderately engorged. Spleen about two-thirds normal size and hard. Mesenteric lymph glands hard, red and translucent. Stomach normal. Duodenum slightly engorged. Small intestine almost normal, except for small patches of congestion. Submucosa appears red. Intestine not ulcerated.

*Microscopic Sections.*—Thymus, pancreas, liver and kidneys are negative. Spleen shows some yellow granular pigment. Mesenteric lymph gland shows many polymorphonuclear leukocytes in its

sinuses. Intestinal mucosa shows no acute inflammation. Epithelium seems normal. Goblet cells and mucus are conspicuous.

Table III is to be contrasted with the two preceding experiments. In this experiment the *spark gap* is only six inches as compared with nine inches in the first two experiments. We may say that the minimum lethal dose with a nine-inch spark gap is about 200 to 210 ma. minutes and with a six-inch spark gap is about 450 to 500 ma. minutes. The nine-inch spark gap, of course, represents an electric current of much higher voltage and the constitutional effect of such a current is much greater than a lower voltage current with smaller spark gap.

The dog was profoundly intoxicated on the fourth day and death seemed very probable. An intravenous injection of hypertonic glucose solution containing calcium lactate was given, with temporary benefit. There was a remarkable retention or sparing of nitrogen on the following day, as shown by the urinary nitrogen. An identical procedure was carried out forty-eight hours later. The dog was sacrificed on the seventh day, as there was no hope of recovery from the intoxication.

The blood non-protein nitrogen was unusually high in this animal and an explanation is given by the autopsy. There was conclusive evidence of septicemia, with pulmonary and submucous ecchymoses, small infarct in adrenal and tiny focal abscesses in the kidneys. There were areas of inflammatory reaction in the gastric and intestinal mucous membrane. We may assume that epithelial injury associated with the profound systemic intoxication allowed the intestinal bacteria to invade the mucous membranes and blood stream.

TABLE III.—17-172—ROENTGEN RAY, LETHAL DOSE.

Date.	Weight, pounds.	Urine, c.c.	Nitrogen, grams.	Diet.	Remarks.
April 1	33.00	435	2.91	400 c.c. water 100 gm. sugar	Dog normal.
2	32.25	390	2.80	"	
3	31.75	462	3.02	"	
3	Roentgen ray—	500 ma. min.,	2 mm. aluminum filter, spark gap 6 inches.		
4	30.81	370	3.53	400 c.c. water 100 gm. sugar	Dog normal.
5	30.00	622*	3.36	"	Slight vomitus.
6	29.00	653*	5.26	"	Much vomitus; dog very sick.
7	27.44	977*	7.73	400 c.c. water in cage	570 c.c. glucose solution, 10 per cent. containing 0.2 gm. calcium lactate.
8	27.00	743*	2.58	400 c.c. water in cage	Diarrhea; little vomitus.
9	26.70	609*	9.41	400 c.c. water in cage	550 c.c. glucose solution, 10 per cent. containing 0.2 gm. calcium lactate.
10	26.50	818*	3.72	....	Profound intoxication.
10		Sacrifice—Blood	non-protein nit	rogen = 201 mg.	

\* Urine contains vomitus.

*Autopsy* (Dog 17-172, Table III). Heart and thorax normal. Lungs are speckled with small hemorrhagic areas not over 1 to 2 mm. in diameter. Spleen and liver negative. Kidneys show a few opaque specks, probably abscesses in cortex and pyramids. Pancreas and thyroid somewhat congested. Bladder shows a catarrhal cystitis. Stomach and intestines show occasional submucous hemorrhages.

*Microscopic Sections.* Lung shows areas of hemorrhages and a few patches of leukocytic exudate, involving only small groups of acini. Spleen shows much blood pigment and a decrease in pulp cells. Malpighian bodies are not decreased in size but leukocytes are scanty in pulp. Liver shows a little cloudy swelling. Adrenal shows a small-sized infarct about 3 mm. in diameter. Kidneys show a very few tiny linear abscesses. The tubular epithelium shows some degeneration but no necrosis. Stroma normal. There are a few hyaline casts. Testes contain spermatozoa. Stomach shows definite inflammatory reaction of mild grade in its mucosa, with invasion of polymorphonuclear leukocytes. There is slight edema, but no obvious epithelial necrosis. Small intestine shows occasional small areas of early inflammation.

TABLE IV.—18-71—ROENTGEN RAY, LETHAL DOSE.

Date.	Weight, pounds.	Urine, c.c.	Nitrogen, grams.	Diet.	Remarks.
Dec. 4	13.87	306	2.24	300 c.c. water	Dog normal.
5	13.43	338	2.24	300 "	
6	13.19	331	2.46	300 "	
6	Roentgen ray—210 ma. min., 2 mm. aluminum filter, spark gap 9 inches.				
7	12.75	295	2.43	300 c.c. water	Dog normal.
8	12.38	361	2.55	300 "	Dog normal.
9	11.87	401	3.64	300 "	Vomiting.
10	11.38	295	5.04	200 "	Vomiting; black diarrhea; dog very sick.
11	11.19	226	3.72	265 "	Clinical improvement.
12	11.06	206	3.70	230 "	Clinical improvement.
13	10.87	262	3.47	200 "	No diarrhea.
14	10.31	232	3.14	200 "	Diarrhea.
15	10.19	225	3.14	325 "	Diarrhea marked.
16	Found	dead—vomitus in	cage.		

Table IV illustrates a temporary recovery from the general intoxication following a dose of 210 ma. minutes with nine-inch spark gap. As usual the dog was profoundly intoxicated on the fourth day following the roentgen-ray treatment. There were prostration, vomiting and bloody diarrhea. Then came a period of clinical improvement for three days, followed by two days of intoxication and death.

It is clear from the autopsy that this dog was about to recover from the specific roentgen-ray intoxication which reached its maximum as usual on the fourth day, just short of a lethal intoxication. The

autopsy showed many ecchymoses in the liver, kidneys and intestinal mucosa. The liver showed typical focal hyaline necroses probably not over forty-eight hours of age. There was epithelial degeneration in the kidneys. The mucosa of the small intestine showed an early inflammatory reaction, with slight edema and inwandering of polymorphonuclear leukocytes. It is possible that intestinal bacteria gained entrance to the blood stream through this damaged mucosa and caused the focal liver necroses and fatal terminal intoxication. This gives some evidence which may be interpreted to mean a definite but delayed injury of the mucous membrane of the intestine due to the roentgen rays. Some observers may wish to explain this apparent injury to the intestinal mucosa as being purely mechanical and the direct result of the violent diarrhea and vomiting of the preceding days. It is known that vigorous purgation in some animals may be associated with the appearance of intestinal bacteria in the blood stream.

TABLE V.—18-3—ROENTGEN RAY, SUBLETHAL DOSE, SLIGHT CLINICAL REACTION.

Date.	Weight, pounds.	Urine, c.c.	Nitrogen, grams.	Diet.	Remarks.
Nov. 14	37.25	520	3.25	400 c.c. water 100 gm. sugar	Dog normal.
15	36.50	460	2.69	"	
16	35.75	537	2.94	600 c.c. water 100 gm. sugar	
16	Roentgen ray—200 ma. min., 2 mm. aluminum filter, spark gap 9 inches.			400 c.c. water 100 gm. sugar	Dog normal.
17	35.31	671	3.86	"	Dog normal.
18	35.43	550	3.47	"	Given some food in error.*
19	35.00	486	3.11	"	
20	34.37	955	4.76*	"	Little vomitus.
21	33.75	480	2.94	"	
22	33.19	509	3.39	"	
23	32.5	525	3.81	"	
24	32.06	596	4.20	....	Dog perfectly normal.

*Autopsy* (Dog 18-71, Table IV). Heart, lungs and thorax normal. Spleen less than two-thirds normal size and fibrous. Pancreas and adrenals normal. Kidneys specked with tiny red dots. Cortex is pale and architecture normal. Liver specked with orange-yellow dots and ecchymoses. Portal tissue is swollen and conspicuous. Stomach normal. Duodenum and jejunum show slight congestion. Ileum and colon present more marked congestion of the mucous membrane and some ecchomoses in the colon.

*Microscopic Sections.* Liver shows scattered focal hyaline necroses which involve parts of lobules and are not more than two days of age. Kidneys show little epithelial degeneration in the convoluted tubules. Pancreas and stomach normal. Ileum shows

slight edema of villi in places and increase in polymorphonuclear leukocytes. Evidently, in this case, there was an invasion of the blood stream by bacteria from the intestine during the last two or three days of life. This seems to be the best explanation of the liver necrosis and inflammatory reaction in the intestinal villi. Whether this reaction was primarily due to mechanical or roentgen-ray injury of the intestinal epithelium is open to debate.

Table V presents the data of an experiment with a sublethal dose of the roentgen rays. This dose of 200 ma. minutes may be considered as very close to the minimum lethal dose. This was a very active and strong dog, which may explain some of the individual tolerance. The increase in urinary nitrogen is definite for three days, but not extreme, and the clinical reaction is practically negative. Yet we can be sure from other experiments that a slight increase in the dosage would have precipitated a fatal reaction.

TABLE VI.—DOG 17-165—NEGATIVE ROENTGEN-RAY ANAPHYLAXIS.

Date.	Weight, pounds.	Urine, c.c.	Nitrogen, grams.	Diet.	Remarks.
April 14	23.63	337	2.66	400 c.c. water	Dog normal.
15	23.13	441	2.72	400 "	
16	22.88	414	2.69	...	500 c.c. glucose solution; 10 per cent. intravenously.
17	22.19	691	2.24	400 c.c. water	
18	21.94	339	2.77	...	500 c.c. glucose solution; 10 per cent. intravenously.
19	21.69	504	2.18	400 c.c. water	
20	21.50	712	2.02	400 "	
20	Roentgen ray—360	ma. min., 2 mm. aluminum filter, spark gap 6 inches.			
21	21.06	408	3.14	400 c.c. water	No clinical symptoms.
22	20.75	422	3.14	400 "	Normal.
23	20.38	473	2.58	400 "	
24	20.25	372	2.55	400 "	
25	20.06	397	2.49	400 "	
26	19.88	378	2.35	400 "	
			Second observation.		
May 10	22.69	438	2.02	400 c.c. water	Dog normal.
11	22.31	407	1.74	400 "	
11	Roentgen ray—300	ma. min., 2 mm. aluminum filter, spark gap 6 inches.			
12	21.69	512	2.74	400 c.c. water	No clinical symptoms.
13	21.38	366	2.86	400 "	Dog normal.
14	21.06	452	2.10		
15	20.69	436	2.21	400 c.c. water	
16	20.56	385	2.02	400 "	
17	20.25	407	2.07	400 "	Dog normal.

That roentgen-ray anaphylaxis does not exist in dogs is clearly shown in Tables VI, VII and VIII. Table VI confirms the data in Table V to show that a dose of roentgen rays equivalent to 75 per cent. of the lethal dose or more may not disturb the nitrogen elimination in any considerable degree. The slight rise in urinary nitrogen appears in the two days following the roentgen-ray exposure

in both the primary and secondary observation. There is no difference in the nitrogen curve in either case and no clinical reaction. The data relating to the glucose injections is included for the sake of comparison with an experiment above. (See Table III.)

Table VII gives confirmatory data for the preceding experiment. The first dose is accompanied by considerable vomiting and diarrhea, but no signs of severe intoxication and little increase in the urinary excretion of nitrogen. A part of the reaction may be explained by the possibility that the sugar solution was somewhat irritating to this animal. There can be little doubt that a major part of the clinical reaction was due to the roentgen rays. The second dose caused no clinical reaction and little increase in urinary nitrogen. This exposure was shorter than the first but sufficiently large to rule out any anaphylaxis or even summation of intoxication, as the two roentgen-ray doses together are much over a lethal dose.

TABLE VII.—DOG 17-157—NEGATIVE ROENTGEN-RAY ANAPHYLAXIS.

Date.	Weight, pounds.	Urine, c.c.	Nitrogen, grams.	Diet.	Remarks.
Mar. 6	17.44	411	1.90	75 gm. sugar 400 c.c. water	Fasting four days.
7	17.06	381	1.93		Dog normal.
8	16.75	376	1.76	"	
8	Roentgen ray—400 ma. min., 2 mm. aluminum filter, spark gap 6 inches.				
9	16.25	Lost	..	75 gm. sugar 400 c.c. water	
10	16.00	383*	1.62		45 c.c. vomitus; diarrhea.
11	15.50	455*	1.96	"	Vomitus in urine.
12	15.06	291*	2.30	"	210 c.c. vomitus; diarrhea.
13	14.88	624*	1.74	"	Vomitus.
14	14.88	206*	2.02	"	430 c.c. vomitus; diarrhea.
15	14.88	395	1.62	"	Solid feces.
16	14.50	351	1.43	"	
17	14.38	380	1.40	"	Clinical improvement.
Second observation.					
April 28	16.94	..	..	400 c.c. water	Dog normal.
29	16.50	424	2.07	400 "	
30	16.19	331	1.96	400 "	
30	Roentgen ray—300 ma. min., 2 mm. aluminum filter, spark gap 6 inches.				
May 1	15.75	457	2.04	400 c.c. water	No clinical reaction.
2	15.50	287	2.13	400 "	
3	15.13	408	2.10	400 c.c. water	Normal.
4	14.88	438	1.93	400 "	
5	14.50	411	2.04	400 "	Little diarrhea and vomitus.
6	14.31	401	1.82	400 "	
7	14.06	393	1.96	400 "	Dog normal.

\* Vomitus and urine combined for N analysis

The experiment outlined in Table VIII is somewhat different in character, but the evidence against the roentgen-ray anaphylaxis is just as convincing. The first dose is relatively small (three-fifths of lethal with six-inch spark gap) and is followed by only a very

slight rise in the curve of nitrogen excretion, lasting three or four days. The second dose was practically twice a lethal dose, given by mistake, as the nine-inch spark gap was not taken into the calculation. In spite of the large dose and the preceding roentgen-ray exposure, the dog showed the usual latent period of two days during which there were no clinical symptoms. Death as usual followed on the fourth day, with the usual autopsy findings described above.

TABLE VIII.—DOG 18-36—NEGATIVE ROENTGEN-RAY ANAPHYLAXIS, SECOND DOSE LETHAL.

Date.	Weight, pounds.	Urine, c.c.	Nitrogen, grams.	Diet.	Remarks.
Sept. 15	24.00	395	2.30	400 c.c. water	Dog normal.
16	23.63	355	2.35	400 "	
17	23.00	370	2.49	400 "	
18	22.94	365	2.55	400 "	
19	22.63	437	2.24	400 "	
20	22.38	369	2.16	400 "	
20	Roentgen ray—300 ma. min., 2 mm. aluminum filter, spark gap 6 inches.				
21	22.00	445	2.35	400 c.c. water	
22	21.63	432	2.86	400 "	
23	21.31	410	2.58	400 "	
24	21.06	196	2.38	400 "	
25	20.81	385	2.11	400 "	
26	20.50	393	2.13	400 "	
27	20.06	382	2.04	400 "	
28	19.88	378	1.99	400 "	
29	19.44	366	2.02	400 "	Normal.
Second observation					
Oct. 13	21.63	475	1.91	400 c.c. water	Dog normal.
14	21.25	368	1.82	400 "	
15	21.06	387	2.04	400 "	
15	Roentgen ray—400 ma. min., 2 mm. aluminum filter, spark gap 9 inches.				
16	20.25	575	3.19	400 c.c. water	
17	19.81	375	2.88	400 "	Dog normal; no vomitus.
18	19.13	598	3.64	400 "	Vomitus; dog not very sick.
19	Dead	575	2.02	....	Much bloody diarrhea in cage.

*Autopsy* (Dog 18-36, Table VIII). Heart, lungs and thorax normal. Spleen small and hard. Liver deep red and congested. Pancreas normal. Kidneys much congested; architecture normal. Stomach full of thin straw-colored fluid and mucosa normal. Duodenal mucosa deep red, congested and bile-stained. Jejunum and ileum show decreasing congestion of mucosa as the ileocecal region is reached. Colon shows red longitudinal ridges in its mucosa, and it is tightly contracted. Capillary engorgement of the viscera and intestinal tract is the only noteworthy abnormality.

*Microscopic Sections.* The intestinal mucosa in places shows definite hemorrhages and some epithelial degeneration, although complicated by postmortem degeneration.

The absence of any constitutional reaction associated with the



roentgen-ray burn is clear from the data included in Tables IX and X. Table IX shows a long latent period following the roentgen-ray exposure and the dermatitis which later developed into an ulcer or "burn." During the latent period there is no evidence of any increase in protein breakdown, and the nitrogen excretion is constant. When the skin is broken and moist following the dermatitis we note a slight rise in urinary nitrogen, which is due to the inflammatory reaction in the skin.

TABLE IX.—17-209—ROENTGEN-RAY BURN, NITROGEN METABOLISM UNDISTURBED.

Date.	Weight, pounds.	Urine, c.c.	Nitrogen, grams.	Diet.	Remarks.
Sept. 19	23.00	369	2.24	400 c.c. water	Dog normal.
20	23.25	418	2.16	400 "	
20	Roentgen ray—100 ma. min., no filter, spark gap 6 inches, left chest.				
21	22.81	426	2.24	400 c.c. water	Dog normal.
22	22.44	384	2.19	400 "	
23	22.0	410	2.13	400 "	
24	21.81	418	2.04	400 "	
25	21.25	431	1.71	400 "	
26	21.06	399	2.02	400 "	
27	20.56	393	1.88	400 "	
28	20.38	414	2.07	400 "	
29	20.19	369	1.90	400 "	
30	..	..	2.04	400 "	
Oct. 1	19.50	456	1.71	400 "	Skin is normal.
2	19.13	446	1.57	100 gm. sugar 400 c.c. water	
3	19.25	358	1.29	"	
4	19.13	307	1.04	"	
5	19.06	356	1.57	"	Slight dermatitis and loss of hair.
6	19.06	375	1.12	"	
7	18.94	387	1.23	"	
8	18.75	407	1.23	"	
9	18.63	406	1.23	"	
10	18.50	424	1.29	"	Skin moist and tender.
11	18.25	417	1.31	"	
12	18.13	414	1.26	"	
13	17.94	382	1.34	Mixed diet	Dog active and lively; roentgen-ray burn is moist and somewhat tender.
17	19.19	Sacrifice		"	

*Autopsy* (Dog 17-209, Table IX). The organs are normal.

*Microscopic Sections.* Microscopic sections add nothing of importance. There is little reaction in the superficial skin lesion due to the roentgen rays.

The data in Table X is not quite so satisfactory as that given above (Table IX), but in general confirm the preceding experiment. There are periods of slight increase in urinary nitrogen after both roentgen-ray exposures, but there was clinical evidence of a very slight distemper which can modify the nitrogen elimination. The

latent period here was about three weeks between exposure to the roentgen rays and development of the "burn" or ulcer.

TABLE X.—17-134 (1)—ROENTGEN-RAY BURN, DELAY IN REACTION.

Date.	Weight, pounds.	Urine, c.c.	Nitrogen, grams.	Diet.	Remarks.
Feb. 17	15.75	211	1.26	100 gm. sugar 400 c.c. water	Dog normal.
18	15.50	327	1.29	"	
19	15.44	331	1.09	"	
20	15.25	313	1.12	"	
20	Roentgen ray—50 ma. min.			n., no filter, spark gap 6 in., left hind quarter.	No clinical symptoms.
21	15.25	303	1.18	100 gm. sugar 400 c.c. water	
22	15.06	400	1.23	"	
23	15.00	297	1.12	"	
24	14.94	336	1.29	"	
25	14.81	321	1.18	"	
26	14.69	346	1.40	"	
27	14.56	328	1.23	"	
28	14.38	353	1.29	"	
Mar. 1	14.00	393	1.23	"	
1	Roentgen ray—80 ma. min.			n., no filter, spark gap 6 in., right hind quarter.	Evidences of very slight distemper.
2	13.75	368	1.29	100 gm. sugar 400 c.c. water	
3	13.25	548	1.57	"	
4		386	1.68	"	
5	12.69	468	1.62	"	
6	12.50	460	1.51	"	
7	12.38	447	1.51	"	
8	12.25	460	1.34	"	
9	12.19				
10	12.69	133	1.34	"	
11	12.63	347	1.15	"	Skin everywhere normal.
17	Dermatitis left leg.				Dog active and eats well.
20	Early ulcer right leg.				

The question of tolerance to the roentgen rays is raised by the experimental data of Tables X and XI. This dog was exposed to the unfiltered roentgen rays on two occasions to produce a burn or roentgen-ray ulcers. Three months later the dog was given a supposedly lethal dose (500 ma. minutes, six-inch spark gap). For a dog of this size the dose was considered surely lethal. The dog was very sick and showed all signs of a very severe intoxication—vomiting, diarrhea, prostration, leukopenia and some increase in blood non-protein nitrogen. The severest symptoms appeared on the fourth day, and after this there was slow improvement to complete recovery. The urinary nitrogen shows much increase, especially on the fourth and fifth days, when it was over twice normal. We may say that this dog had developed a very slight tolerance to the general roentgen-ray intoxication following the two previous exposures, or that this dog presented an abnormally high individual resistance to the intoxication.

TABLE XI.—17-134 (2)—ROENTGEN-RAY INTOXICATION,  
TOLERANCE (?) TO LETHAL DOSE.

Date.	Weight, pounds.	Urine, c.c.	Nitrogen, grams.	Diet.	Remarks.
May 29	15.56	340	1.96	400 c.c. water	Both legs show roentgen-ray ulcers. (See Table X.)
30	15.13	395	2.26	400 "	Dog active.
31	14.94	338	2.24	400 "	
31	Roentgen ray—500 ma. min., 2 mm. aluminum filter, spark gap 6 inches.				
June 1	14.50	391	2.80	400 c.c. water	White blood cells, 17,000.
2	14.13	417*	2.86	400 "	Vomit.
3	13.56	641*	3.70	520 "	Vomit; diarrhea.
4	12.75	632*	5.60	400 "	Dog very sick; white blood corpuscles, 2700; vomitus; diarrhea; blood N. P. N., 47 mg.
5	12.50	350	4.48	225 "	Vomit and diarrhea.
6	12.56	187	5.26	400 "	Diarrhea.
7	12.06	385	3.30	400 "	Dog better.
8	12.06	75	2.41	....	Dog will recover.
8	Sacrifice. Blood N. P. N., 29 mg.				

\* Urine contained vomitus.

(Dog 17-134 (2), Table XI). This dog was exposed to the roentgen rays on February 20 (50 ma. minutes) and March 1 (80 ma. minutes). Spark gap six inches; no filter in each instance. Dermatitis appeared over the first area on March 17 and over the second area on March 20. Ulcers slowly developed, which tended to heal slowly in the following weeks. The dog was in excellent health, with good appetite and general activity.

June 8. Sacrifice by ether and bleeding. *Autopsy* at once. The organs of this dog were washed free from blood by the use of normal saline and various catalase determinations done. There seemed to be no striking abnormalities in gross.

*Microscopic sections* add nothing of importance.

TABLE XII.—DOG 18-72—CHLOROFORM AND ROENTGEN-RAY  
INTOXICATION.

Date.	Weight, pounds.	Urine, c.c.	Nitrogen, grams.	Diet.	Remarks.
Dec. 4	18.13	480	2.63	400 c.c. water	Dog normal.
5	17.56	398	2.88	400 "	
6	17.25	437	2.46	400 "	
6	Chloroform anesthesia, 1 hour.				
7	16.13	165	4.70	400 c.c. water	Dog not intoxicated.
7	Roentgen ray—200 ma. min., 2 mm. aluminum filter, spark gap 9 inches.				
8	15.75	345	5.32	400 c.c. water	Dog is much intoxicated.
9	15.56	325	4.59	300 "	Vomit and diarrhea.
10	15.19	381	3.42	110 "	Dog is sick.
11	14.56	195	3.36	200 "	Diarrhea marked.
12	14.50	152	2.97	200 "	
13	14.13	277	2.94	200 "	Clinical improvement.
14	13.81	237	2.97	200 "	
15	13.56	220	2.69	200 "	Dog no longer intoxicated.
16	13.31	305	2.80	200 "	Ether and sacrifice.
16	Blood non-protein nitrogen, 36 mg., and urea N, 26 mg. per 100 c.c.				

Tables XII, XIII and XIV may be considered together. They show convincingly that chloroform poisoning and liver necrosis do not modify the general constitutional reaction to the roentgen rays whether a sublethal or lethal dose be given. Table XII gives the data to show very beautifully the summation in urinary nitrogen elimination, due in part to the chloroform injury and in part to the severe roentgen-ray intoxication. The nitrogen curve does not fall to normal even within ten days and autopsy shows the incomplete repair of the liver necrosis. The roentgen-ray exposure in this experiment (200 ma. minutes, nine-inch spark gap) is very close to the lethal dose; in fact, this may be a lethal dose to some dogs. The clinical reaction is certainly due to the roentgen-ray intoxication and not to the chloroform injury, which is not sufficient in itself to give rise to clinical symptoms.

Tables XIII and XIV show a lethal dose of roentgen ray superposed on a chloroform injury. The chloroform injury in Table XIII was slight because of the sugar feeding, but was moderately severe in Table XIV, a fasting experiment. The chloroform injury was scarcely sufficient to account for any of the clinical symptoms except the icterus (Table XIV). The largest dose of roentgen rays (Table XIV) was responsible for a very clean-cut injury of the epithelium in the intestinal mucous membrane. It is reasonably certain that this injury is due to the roentgen rays and is responsible for the rapid postmortem autolysis of the intestinal epithelium which was described in the preceding experiments. (See Table XIII and I.) This whole picture makes it very unlikely that the roentgen rays have any specific injurious effect on the epithelium of the liver, for the general reaction is not modified in the slightest by the presence of a definite degree of liver necrosis.

TABLE XIII.—DOG 18-33—CHLOROFORM AND ROENTGEN-RAY INTOXICATION.

Date.	Weight, pounds.	Urine, c.c.	Nitrogen, grams.	Diet.	Remarks.
Oct. 21	21.63	470	2.24	400 c.c. water	
22	21.31	420	2.16	400 "	Diarrhea.
23	21.00	452	2.18	75 gm. sugar 700 c.c. water	Blood N. P. N., 37 mg.
24	20.94	620	2.44	75 gm. sugar 300 c.c. water	
25	20.56	438	1.62	"	
25	Chloroform anesthesia, 1 hour.			75 gm. sugar	Diarrhea.
26	19.81	452	2.49	300 c.c. water	Diarrhea.
27	19.81	455	4.62	"	
27	Roentgen-ray, 300 ma. min., 2 mm. alumi			num filter, spark gap 9 inches.	
28	19.06	372	4.93	75 gm. sugar 300 c.c. water	Diarrhea; dog sick.
29	18.75	653	5.10	"	Vomitus; dog sick; blood N. P. N., 41 mg.
30	18.06	507	4.93	"	Vomitus and diarrhea; blood N. P. N., 52 mg.
31	Dead	965	3.89	....	Bloody vomitus; diarrhea.

*Autopsy* (Dog 18-72, Table XII). Heart, lungs and thorax normal. Spleen tough and fibrous, about two-thirds normal size. Pancreas, adrenals and kidneys normal. Stomach and intestinal tract normal. Liver below normal in size, tough and fibrous. Lobules show depressed centers, which are red. The mid-zone of each lobule is yellowish and contains fat. The peripheral or portal zone is gray and translucent. Gall-bladder is distended.

*Microscopic Sections.* Liver shows incomplete repair of the chloroform injury, which probably involved about one-third to one-half of each lobule. Spleen, kidney and intestine negative.

*Autopsy* (Dog 18-33, Table XIII). Heart, lungs and thorax normal. Spleen thin and hard. Pancreas normal. Liver dark red and congested. Section is gelatinous and translucent. No evidence of chloroform necrosis. Kidneys normal except congestion. Stomach and intestinal tract show a little postmortem change, but definite congestion of the mucous membranes is most marked in the duodenum and jejunum. No ulcers and no definite hemorrhages.

*Microscopic Sections.* Spleen and pancreas are normal. Kidney shows cloudy swelling of the convoluted tubules. Liver is normal. The sugar evidently protected the liver against the chloroform injury or the repair of the injury was complete. Stomach normal. Small intestine shows much autolysis of the epithelium in the crypts as described above. (Dog 18-45, Table I, Autopsy.) There is an increase in polymorphonuclear leukocytes in the stroma of the mucous membrane, which indicates a definite antemortem injury done to structures in this mucosa.

TABLE XIV.—DOG 18-46—CHLOROFORM AND ROENTGEN-RAY INTOXICATION.

Date.	Weight, pounds.	Urine, c.c.	Nitrogen, grams.	Diet.	Remarks.
Oct. 2	25.63	461	2.13	400 c.c. water	
3	25.13	466	2.21	400 "	Blood N. P. N., 35 mg.
4	24.44	371	2.44	400 "	Diarrhea.
4	Chloroform anesthesia, 1 hour.				
5	23.88	432	3.53	400 c.c. water	No clinical intoxication.
5	Roentgen ray, 400 ma. min., 2 mm. aluminum filter, spark gap 9 inches.				
6	23.38	545	4.65	400 c.c. water	Dog is dull.
7	22.38	630	7.79	400 "	Dog is dull.
8	21.31	445	9.25	400 "	Vomitus; bloody diarrhea; icterus; dog very sick.
9	21.06	506	7.18	.....	Dog very sick; sacrificed.
	Dog would die in a few hours; blood N.				P. N., 100 mg.

*Autopsy* (Dog 18-46, Table XIV). Icterus marked. Blood clots in normal time and clots are rather soft. No ecchymoses in tissues. Heart, lungs and thorax normal. Spleen small and fibrous. Kidneys and pancreas normal. Mesenteric glands deep red and moist. Liver very yellow and fatty. Lobulation uniform, with red centers,

fatty mid-zone and translucent marginal or portal zone. Stomach contains blood-tinged fluid. Mucosa slightly swollen and deep pink color. Duodenum shows a deep pink mucosa and contains much blood-tinged fluid. Very little mucus. Small intestines are moderately contracted. There is definite congestion of the mucous membrane, but little mucus secretion. Colon shows the same congestion and contains thin blood-tinged feces.

*Microscopic Sections.* Spleen, kidney and adrenals negative. Liver shows hyaline necrosis involving about one-half of each lobule. There has been practically no repair of this injury, which usually proceeds so rapidly. This is due in part to fasting and in part to the roentgen-ray treatment. Small intestines in many places show definite injury of the epithelium lining the crypts and accumulation in such areas of clusters of polymorphonuclear leukocytes. There is little if any edema of the interstitial tissue, but some increase in polymorphonuclear leukocytes. Colon shows great increase in mucous accumulation in its crypts and some epithelial injury and groups of polymorphonuclear leukocytes.

TABLE XV.—SUMMARY OF ROENTGEN-RAY INTOXICATION EXPERIMENTS.

Experiment No.	Roentgen ray.		Delay in clinical reaction (days).	Blood.		Death after roentgen-ray exposure (days).	Remarks.
	Milli-ampère min.	Spark gap, inches.		Non-protein nitrogen, mg. per 100 c.c.	Urea nitrogen, mg. per 100 c.c.		
18-45	500	9	1.0	50*	..	3.5	
18-69	220	9	2.5	59	24	4.0	
18-71	210	9	2.0	..	..	9.5	
18-52	380	9	1.0	47*	..	3.5	
18-55	300	9	2.0	58*	..	3.5	
18-61	300	9	2.0	78	49	4.0	
17-10	500	6	0.5	168	102	3.0	
17-172	500	6	1.5	201	..	7.0	
16-110	500	6	0.5	172	94	7.0	Renal calculus.
17-134	500	6	1.0	29	..	Recovery	Tolerance (?).
18-72	200	9	..	36	26	Sacrifice	Chloroform added.
18-46	400	9	..	100	59	4.0	Chloroform added.
18-33	300	9	..	52*	..	3.5	Chloroform added.
18-36	300	6	Neg.	..	..	..	No intoxication.
18-36	400	9	2.5	40*	..	3.5	Second exposure.
17-157	400	6	1.0	..	..	Recovery	Severe intoxication.
17-157	300	6	Neg.	..	..	"	Second exposure.
17-165	360	6	Neg.	..	..	"	No intoxication.
17-165	300	6	Neg.	..	..	"	Second exposure.
18-43	160	9	2.5	..	..	"	Slight intoxication.
18-3	200	9	4.0	..	..	"	Slight intoxication.

\* Blood obtained on day before death.

A summary of all the experiments described above is given in Table XV. This table brings out many interesting points and emphasizes particularly the latent period, during which time the dog

appears to be perfectly normal—a latent period of twenty-four to forty-eight hours, as a rule. The clinical intoxication appears suddenly and runs a stormy course, usually resulting fatally on the fourth day. The blood non-protein and urea nitrogen are usually much increased above normal on the day before death or a few hours before death or sacrifice.

The most striking point about the roentgen-ray intoxication brought out in Table XV concerns the length of spark gap. It is very obvious that the rays from the nine-inch spark gap are very much more toxic than those from the six-inch spark gap. This is of considerable practical importance, and is not generally recognized.

#### DISCUSSION.

Let us review in a few words the *clinical picture* of the general constitutional reaction following a suitable exposure of a dog to the filtered hard roentgen rays of the Coolidge tube. The striking latent period is almost always present and may last twelve to twenty-four hours, or even two days, during which time the dog is lively, active and normal to careful examination. There is an increase in urinary nitrogen excretion during this period, indicating that tissue injury and disintegration have already taken place. Gastro-intestinal symptoms are the conspicuous feature of these cases, vomiting and diarrhea becoming marked after the latent period and bearing no relation to food intake. There is usually complete loss of appetite, but water is taken eagerly. The intoxication and general depression may appear after twelve hours, but much more frequently after twenty-four to forty-eight hours. Prostration in fatal cases usually appears on the fourth day, when the initial intoxication reaches its peak and death usually occurs at this time. A few cases pass this period of severe intoxication, show improvement and after three to four days succumb, with recurrence of gastro-intestinal symptoms. In these cases we find evidence of secondary infection which may be relatively slight, but too great a burden for the severely intoxicated animal.

It is remarkable that the maximum intoxication appears so constantly on the fourth day after exposure to the roentgen rays. Even in the experiments in which death came on the seventh, eighth or ninth days there was a period of great clinical intoxication on the fourth day. When the fourth day is safely passed in such experiments we have a right to anticipate complete recovery, although the period of convalescence may be long and the increased nitrogen elimination last seven to ten days. The constancy of this maximum intoxication on the fourth day must have significance in any explanation of this general systemic roentgen-ray intoxication. It is noteworthy that this reaction is independent of size of dose, for death is to be expected on the fourth day whether a single lethal dose or twice a lethal dose be administered.

It is well established by reports of many workers that the general systemic reaction to the roentgen rays is associated with *increased nitrogen elimination* in the urine. This applies to human beings, rabbits, guinea-pigs, rats, mice, dogs, cats, etc. It is usually possible to demonstrate an increase in purin bases and phosphorus radicles in the urine, which indicate the disintegration of cell nuclei, but not necessarily only the nuclei of leukocytes, as some would have us believe. This increase in urinary nitrogen may not be a true index of the severe reaction which may cause fatal intoxication. It is well to recall the curve of nitrogen elimination associated with a sterile abscess (Cooke and Whipple<sup>10</sup>), in which experiment the nitrogen excretion may rise 100 to 200 per cent. or more above the base line. Such an increase dwarfs the considerable nitrogen excretion excess in the roentgen-ray experiments, which rarely show more than 50 to 75 per cent. rise above the base line. Evidently there is a very different type of protein breakdown in these two experiments.

Our experiments show a definite increase in the *non-protein nitrogen* of the blood. This rise is usually distinct on the day before death (even twice normal) and may reach a very high level on the day of death (even more than 100 mg. per 100 c.c. blood). It is clear there is an increased breakdown of body protein, but this alone may not explain the heaping up of nitrogenous split products in the blood, for there may be faulty elimination. It has been claimed by many that the roentgen-ray intoxication is associated with or even in part due to a roentgen-ray nephritis, but the evidence for a true nephritis will not bear careful scrutiny. Many careful workers report negative findings, and others at the most report a little injury of the tubular epithelium in some experimental animals. There is little or no evidence of any nephritis from a study of the urine. We can state that our animals gave no evidence of any nephritis due to the roentgen rays nor even any constant anatomical changes which we could recognize in the renal epithelium. However, this does not rule out an impairment of renal function as a possibility even in the absence of histological evidence. Some work done in this laboratory by Mr. McQuarrie will show that certain proteoses can injure the renal cells to such a degree that renal function may be depressed below one quarter of normal for many hours followed by slow recovery to normal. Even the finest histological technic and vital stains cannot give evidence of any anatomical injury to account for this remarkable impairment of function. We hope to study the roentgen-ray intoxication in a similar fashion and to report on these experiments in the near future.

*Anatomical changes* certainly are not conspicuous in animals dead from the constitutional roentgen-ray intoxication. The spleen is decreased in size, fibrous and contains fewer lymphocytes than normal. Bone-marrow shows a decrease in cells. The parenchymatous organs may be passed over as normal, as there are no



constant abnormalities in gross or under the microscope. The striking symptoms are gastro-intestinal, and the entire tract was examined with much care in all our experiments. The contents may be slightly blood-tinged or even quite dark in the colon, but there are no ulcers of any kind. The stomach usually is normal in gross and microscopically. The small intestine in fatal cases usually shows a mottled mucosa, with patches of congestion often more marked in the jejunum. These patches are very indefinite and shade off into the normal mucosa, but there is distinct engorgement of the capillaries and villi in such areas. The colon may show some patchy congestion and may be tightly contracted. The small intestine has a tendency toward spastic contraction. The *intestinal tract* shows certain abnormalities, concerning which we are not quite satisfied. More work is needed in this field, and we hope to get more data in the near future. Certain experiments in which large doses of the roentgen rays were given show slight but definite abnormalities in the intestinal mucosa. Some of the crypts show degenerated epithelium and large clumps of polymorphonuclear leukocytes grouped about this epithelium and in the mucosa close to the basement membrane of the crypt. The tips of the villi were not included in this reaction. Furthermore, certain experiments showed a most remarkable speed of *autolysis of the intestinal epithelium*. Dogs which were autopsied six to twelve hours postmortem, whose organs showed a minimum degree of postmortem change, presented remarkable histological sections of the intestinal mucosa. The intestinal epithelium had *completely* autolyzed and vanished, leaving only a few epithelial fragments. Such changes cannot be due to the ordinary postmortem changes observed in intestines, as these changes involve the surfaces first, especially the tips of the villi, and spare at first the depths of the crypts. We feel that these observations furnish evidence that these epithelial cells are injured in some way during life and that this injury may be in part responsible for the dominant gastro-intestinal symptoms. One might postulate a very unstable equilibrium of the ferment-antiferment balance due to roentgen-ray exposure, but the term *injury* is just as intelligible. It is admitted that cancer cells and spleen cells are injured by the roentgen rays, and after exposure many of these cells vanish by autolysis *in vivo*. Also, it is known that cancer cells and spleen cells *in vitro* will autolyze faster after exposure to the roentgen rays.

We know that disturbances of the intestinal epithelium react promptly with the production of intoxication—for example, volvulus, intussusception and obstruction. If there is a constant and definite injury of intestinal epithelium caused by the roentgen rays we have a good basis for the clinical intoxication and gastro-intestinal symptoms as well as a new lead by which to study the general disturbances of the intestinal mucous membrane.

*Roentgen-ray anaphylaxis* is a term which has appeared recently in the literature (Bergonie<sup>4</sup>) to indicate a greatly increased sensitiveness to the roentgen rays after a time interval of weeks following the first exposure. Our experiments prove there is no such anaphylaxis nor is there even any difference in the nitrogen excretion, which is a more delicate index for sublethal doses of the roentgen rays than are the clinical symptoms. Whether there may be a certain amount of "summation effect" of the roentgen rays we cannot say with certainty. It is probable that a second dose of the roentgen rays given before the first reaction had subsided would give a more profound reaction. This period of reaction and increased nitrogen elimination may last seven to ten days, and at times even longer, but we have no evidence that a second dose of the roentgen rays given *after* this reaction period may cause any summation effect, anaphylaxis or other unusual reaction. We have some evidence that a very low-grade *tolerance* may develop following repeated exposure to the roentgen rays, but the margin of safety is very low and may come within individual variation to the roentgen-ray treatment.

*Chloroform necrosis* of the liver was combined with roentgen-ray injury because of several interesting possibilities. It has been suggested that the roentgen rays act primarily upon ferments, and consequently upon the cells which are richest in cell ferments. It is known that the liver cells are very rich in ferments and it is very easy to cause a necrosis of one-half of each liver lobule by a suitable dose of chloroform. Some liver cells which escape necrosis are damaged, and possibly as a result are more susceptible to other agents which injure liver cells. Superimposing a maximal sublethal roentgen-ray dose upon a chloroform liver of this sort should give a modified reaction if the liver takes a prominent part in this reaction. (See Table XII.) The reaction is not modified by the presence of the chloroform necrosis of the liver, but the nitrogen elimination shows a very pretty summation of the chloroform injury plus the roentgen-ray reaction. This is strong evidence surely that the liver does not play any essential part in the constitutional reaction to the roentgen rays.

This general systemic reaction which may follow the use of the roentgen rays in therapeutic doses has another appeal to the investigator. This reaction must be "*non-specific*," as no group of bacteria can possibly be concerned. If any injurious substances are formed in the body these substances must be formed from body tissues or fluids and not from any protein substances introduced. It seems safe to assume that the body protein must be injured in some fashion, as there is a distinct increase in urinary nitrogen and in the non-protein nitrogen of the blood. In fact, the primary injury may react upon the body protein in some manner so that the tissue autolysis of the injured protoplasm may form toxic split products which cause further injury to the body protein—a vicious circle.

The intoxication associated with an acute hemorrhagic pancreatitis is a good example of this type of reaction when the primary injury is inflicted upon parenchyma cells rich in enzymes. It is easy to suppose an autolysis of this protein material by these intracellular enzymes and the formation of toxic split products which may cause even a rapidly fatal intoxication. There are many points in common when we review the picture of roentgen-ray intoxication and of acute pancreatitis.

Intestinal obstruction is another example of a "non-specific" intoxication in which there is a great breakdown of tissue protein, as indicated by the nitrogen elimination in the urine and the accumulation of non-protein nitrogen in the blood (Whipple, Cooke and Stearns<sup>58</sup>). The clinical picture of acute intestinal obstruction presents a remarkable parallel to the clinical story of the fatal roentgen-ray intoxication. Death may take place at about the same interval after the initial roentgen-ray injury or obstruction, violent gastro-intestinal disturbances dominate the picture in both conditions and there is every evidence of great tissue injury and increased tissue katabolism. There is evidence for a perverted secretion (obstruction) or actual injury (roentgen rays) of the intestinal epithelium in these two conditions.

The *sparing action of carbohydrates* is illustrated in Tables III and VI. The glucose solutions are given intravenously during the most acute stage of intoxication (Table III) and cause a remarkable retention of nitrogen as appearing in the next day's urine. Compare with this the reaction in the normal dog (Table VI). More work is to be done to explain this peculiar retention of nitrogen, and we do not wish at this time to advance any explanation. It is to be observed there was some clinical improvement, and this suggests glucose solutions intravenously as proper treatment for severe cases of general intoxication from the roentgen rays.

The *destruction of leukocytes* by the roentgen rays is well known and serves as the best example of the specific susceptibility to the roentgen rays which is exhibited by certain body cells—for example, leukocytes, germinal cells and cancer cells. Earlier workers who recognized the destruction of the leukocytes tried to explain the general intoxication as a result of the leukotoxin or leukoferments which were set free in the blood. One cannot deny that such products resulting from destruction of the leukocytes may be toxic, but the evidence is against this, and it remains for the proponents of this hypothesis to bring some direct evidence. We know that it is possible to destroy leukocytes in enormous number in the circulation by the introduction of certain organ extracts, yet these reactions can scarcely be said to parallel the intoxication resulting from roentgen-ray exposure. It is possible to destroy great numbers of leukocytes in animals in health or in human beings in disease (leukemia) by small doses of the roentgen rays without any signs of

intoxication. The difficult thing to explain is the peculiar *latent period* of the roentgen-ray intoxication.

The *roentgen-ray burn* again offers the obstacle of the *latent period*. There may be a period of three weeks between the roentgen-ray exposure and the subsequent dermatitis, with loss of epithelium and ulcer formation. One may fall back on the sluggish metabolism and slow growth of the epidermis, yet on occasions the growth of this epithelium may be quite rapid (healing of wounds). The solution of this riddle is not yet at hand.

The *spark gap* is to be emphasized from a study of our fatal cases. As the spark gap is increased the voltage of the electric current is raised and the hardness or penetrability of the rays is increased. The fatal dose for a dog is about 500 ma. minutes with a six-inch spark gap, but only 210 ma. minutes with a nine-inch spark gap. We believe that this fact is not clearly recognized by roentgenologists, and it should be repeatedly emphasized.

It should be noted that the experiments with the six-inch spark gap were performed with an old machine with rheostat control. The nine-inch spark gap experiments were performed with a new and more powerful machine having an autotransformer control. In other experiments we expect soon to control these variables and ascertain the actual voltages which may be a more accurate measure for the toxicity of the roentgen rays than is the spark gap.

*Catalase* is a ferment which has been studied by many workers and recently by Burge,<sup>6</sup> who attempts to explain and correlate a variety of life processes with fluctuations in the catalase content of organs. We are not able to follow him in many of his explanations, but it seemed worth while to contrast the catalase content of normal and rayed tissues. A large number of analyses were determined by the usual methods and extracts made in a variety of ways from normal and rayed organs. Many observations were made upon animals which had been exposed to a lethal dose of the roentgen rays. At the death or after sacrifice the organ extracts were made, some after washing the organs free from blood and others containing blood. These analyses were compared with controls done in the same way omitting the roentgen-ray exposure. Animals were fasting and all conditions were uniform. Variations in figures were as great in the controls as in the rayed animals, and we feel that if the catalase determinations have any value they indicate that this ferment is not disturbed by the roentgen rays. In our hands the individual fluctuations in normal animals are so great as to arouse suspicion in our minds as to minor fluctuations under experimental conditions. We feel that all catalase work must be controlled by a large number of check experiments before a proper interpretation of experimental changes can be reached. So far as we are aware, Burge has published very few control experiments in his many papers.

The question of *ferments* and roentgen-ray exposure is a most

important one. When we finish the analysis of the anatomical changes caused by the roentgen rays and the review of the clinical symptoms of intoxication which may be due to the specific action of the roentgen rays on the leukocyte or the intestinal epithelium or the epidermis, we come up against the fundamental question: How do the roentgen rays injure a living cell? It is claimed by Hertwig<sup>22</sup> that the chromatin is first injured and that this injury is the fundamental one. But Richards has shown that the cytoplasm is also injured. Many workers are tempted to leave the morphology of the cell and venture into the field of cellular ferments which is equally difficult, to say the least. One must be very careful in accepting *in vitro* ferment experiments on unicellular organisms or isolated ferments to explain ferment reactions in the living complex of a warm-blooded animal.

Yet there are observations which indicate that the body ferments in the living cells are actually influenced by the roentgen rays. A spleen removed from a rayed animal will show more rapid autolysis than a control (Heile<sup>19</sup>). The same is true for cancer tissue (Neuberg<sup>40</sup>). Our experiments indicate that the same holds for the epithelium of the intestinal mucous membrane exposed to the roentgen rays. Richards<sup>46 46</sup> who has done the best experiments upon the roentgen rays and ferments is able to show *in vitro* that small doses of the roentgen rays accelerate and larger doses inhibit certain ferment action. He does not believe, however, that this direct action of the roentgen rays on ferments is adequate to explain all the reactions of a living cell to the roentgen rays. This conservative opinion should have much weight.

We must not lose sight of the fact that the roentgen rays pick out certain cells with no apparent rhyme or reason. Why, for instance, is the leukocyte injured and the pancreatic cells, which surely are rich in ferments, escape entirely? Simple disturbance of cellular ferments by the roentgen rays cannot explain any such peculiar reaction as this just mentioned. There must be some initial stimulus or injury inflicted upon certain cells of the body and other body cells must be tolerant and escape this injury or stimulus. It is conceivable that the primary injury may form toxic split products which cause the final intoxication, but we have no right to assume this without some evidence, and this experimental evidence has not been submitted.

The word *injury* may be as good as any to indicate our belief that some change has been effected within the cell substance (nucleus or protoplasm). This change may influence, *first*, the cell protoplasm, cell lipoids, cell ferments, etc., but who is to say whether the structure or the ferment is first changed or "injured" by the roentgen ray? We know of many fundamental changes in cells, even fatal changes, which leave no trace that can be detected by modern histological methods. Yet we cannot accept such an instance with-

out question as an example of *primary* injury to the cell ferments. We are too apt to cloak our ignorance by the use of terms which have very little fundamental significance when subjected to analysis.

In the face of these difficulties the authors hesitate to outline the constitutional reaction to the roentgen rays as pictured in their minds and put forward this explanation with a proper regard for possible objections and criticisms. Exposure of a dog to the roentgen rays brings about certain changes (or "injury") in certain of the body cells. In some cells the injury may be evident in a short time (leukocytes) and in other cells the injury may be greatly delayed (epidermis). We cannot explain this latent period. It is at least possible that other body cells may be injured after a longer or shorter latent period depending upon the individual properties of the cells. The nitrogen elimination shows that the cell injury and autolysis begin promptly after exposure to the roentgen rays and continue with a rising curve to the fatal outcome. The blood non-protein nitrogen speaks for the same progressive destruction of body protein. We have evidence that the ferments in certain cells of the body are profoundly altered and take part in the cell destruction beyond a doubt, yet we cannot say that this ferment disturbance is not secondary to some "injury" of cell substance apart from the enzymes. There are individual peculiarities in the reaction of the cells to the roentgen rays which speak for an individuality in the cell reaction and this surely may not of necessity depend upon primary ferment change. The liver and pancreatic cells are rich in ferments yet so far as we know they escape the roentgen-ray injury. The epithelium of the small intestine is closely related to the liver and pancreatic epithelium yet it appears to be "injured" by the roentgen rays. Is this due to a primary injury of ferments? Then how may we explain the immunity of other parenchyma cells which contain similar autolytic ferments?

The obvious "injury" of the intestinal epithelium offers a satisfactory explanation for many of the clinical features of the fatal intoxication—vomiting, diarrhea and prostration. Disturbances of this epithelium can produce a severe intoxication (intestinal obstruction) and for this reason we think the injury of the intestinal epithelium by the roentgen rays plays no small part in the general systemic reaction and intoxication.

#### SUMMARY.

The general constitutional reaction of dogs given a lethal dose of hard roentgen rays from the Coolidge tube is remarkably uniform and constant. A double lethal dose will not modify the clinical reaction. A latent period of twenty-four hours or longer is the rule and during this time the dog is normal except for an excreted urinary nitrogen. Vomiting and diarrhea then dominate the clinical picture until death which as a rule follows on the fourth day.

The blood non-protein nitrogen commonly shows a marked increase (twice normal) on the day before death and often more than three times normal on the day of death.

The elimination of urinary nitrogen is increased on the day following the roentgen-ray exposure and remains high until death, often an increase of 50 to 100 per cent. above the normal base line.

Autopsy findings are: a spleen which is small and fibrous, a moderate grade of congestion and mottling of the intestinal mucous membrane and strong evidence for *epithelial injury* in the intestinal mucosa. The epithelium lining the intestinal crypts may show actual necrosis and invasion of polymorphonuclear leukocytes. This epithelium also shows a remarkable speed of autolysis and may vanish by autodigestion within a few hours postmortem.

The epithelium of the small intestine apparently is sensitive to large doses of the roentgen rays, and the injury of these important cells may furnish the correct explanation of the general intoxication associated with the vomiting and diarrhea.

The so-called roentgen-ray anaphylaxis or hypersensitiveness to a second properly timed roentgen-ray exposure finds no support in our experiments. In fact, there is some evidence for a slightly increased tolerance to the second dose.

Chloroform injury and the associated liver necrosis do not modify the reaction of the dog to large or small doses of the roentgen rays. This is evidence that the liver epithelium is not fundamentally involved in the fatal roentgen-ray intoxication.

Our experiments yield no evidence of roentgen-ray nephritis.

Increasing the width of the spark gap increases the hardness or penetration of the roentgen rays, and this greatly increases the severity of the constitutional reaction and subsequent intoxication.

Burns caused by the roentgen rays are not associated with any distinct increase in urinary nitrogen during the long latent period between the roentgen-ray exposure and the early dermatitis which precedes the actual ulcer. We know of no satisfactory explanation for this long latent period, which may last for three weeks.

This roentgen-ray intoxication or general constitutional reaction is a good example of a "non-specific" intoxication. Much important information can be obtained by further study of this condition and will well repay the effort.

In conclusion, we wish to acknowledge with sincere appreciation the assistance of Dr. H. E. Ruggles, roentgenologist to the University of California Medical School and Hospitals, and the use of facilities placed at our disposal by the University Hospital.

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## THE IMPORTANCE OF THE MOTION FIELD IN COMPARISON WITH THE FORM FIELD IN FAILING VISION.<sup>1</sup>

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GEORGE RIDDOCH,<sup>2</sup> from a study of records of cases of visual defects caused by injury of the occipital region of the cerebrum, makes certain important observations. He shows that:

Movement may be recognized as a special visual perception.

In restricted visual fields from occipital injuries in which some recovery of vision occurs, the first visual stimulus perceived, which can be recorded on a chart as a field, is movement. Therefore, appreciation of movement returns before the object, as such is recognized.

Recovery of vision for movement begins in the peripheral field.

Appreciation of movement and recognition of an object are always dissociated in patients in whom recovery of vision can be demonstrated; the field for the former, which is the more primitive perception, being the larger.

In prognosis this dissociation is a valuable aid, for when it is absent after a few months have elapsed no recovery of vision occurs.

He believes that the elementary visual perceptions of light, of movement, and of an object are dissociated in a manner similar to the dissociation which is known to occur when sensory paths conducting primary somatic sensory impressions of touch, of pain, of temperature are interrupted; by this I understand him to mean that probably distinct fibers are present in the visual system for the transmission of impressions of light, of motion, of form and of color. He mentions that it has long been known that the perceptions of light, of form and of color are to be found dissociated when the visual area is injured, and that it has also been recorded that coarse or even fine movements of the fingers may be detected before the fingers presented in the so-called blind field can be recognized. He states that hitherto the fields for movement have not been systematically charted nor has an attempt been made to inquire into visual dissociations in the light of recent additions to our knowledge of cerebral disturbances of somatic sensation. The whole subject has received greater interest since the investigations of Riddoch.

A patient has recently been referred to me by Major Charles H. Frazier with symptoms clearly permitting the diagnosis of tumor of the pituitary gland; acromegalic features, large feet and hands, etc. The roentgen-ray examination showed enlargement of the sella turcica. The patient, a woman, was admitted to the University

<sup>1</sup> Read before the Philadelphia Neurological Society, January 22, 1919.

<sup>2</sup> *Brain*, 1917, xl, 15.

Hospital, December 31, 1918. She had been under the care of Dr. Edward R. Evans, of Utica, N. Y., who reported that he had found decided choked disks. Each day as he tested for hemianopsia it seemed that objects in the left temporal field were considerably less distinct than in the right field. Vision steadily diminished during two weeks, and when examined by Captain Cross advanced optic atrophy was found in the left eye and much atrophy also in the right eye, with many fresh hemorrhages which probably accounted for sudden loss of vision.

In examining her roughly with the hand, with a black object 6 x 4 inches, or a white hairbrush, I found that with her left eye she saw movement only in the nasal field but could not tell what the object was. She had no vision in the temporal field even for motion. With her right eye alone she recognized a large object in both nasal and temporal fields, but more distinctly in the nasal field. She recognized movement promptly in both nasal and temporal fields of her right eye.

The examination on January 1, 1919, when the day was cloudy and electric light was used, showed that the patient was unable to detect an object at rest with her right eye, but could detect motion vaguely in both nasal and temporal fields of the right eye. At this time she could not detect motion in the nasal field of the left eye.

The examination on January 4, 1919 showed that in bright daylight with the left eye she could not distinguish light from darkness, once she saw a moving object in the nasal field and not at all in the temporal, but she could not see an object when still in either field of the left eye. With the right eye she could see objects still or moving in the nasal or temporal field.

The interesting feature of the visual examination was the ability to recognize movement in the nasal field of the left eye when the sight of the left eye was so far gone that the patient could not recognize form in the nasal field of the left eye and could not recognize either form or movement in the temporal field of the left eye. Even this limited vision was impaired within four days, and soon all vision in both eyes was lost. The recognition of movement only in the nasal field of the left eye conformed with the observation of Dr. Evans that vision first failed in the left temporal field, or at least failed more rapidly. My first examination was made at a time when all recognition of form had been lost in the nasal field of the left eye, while sufficient vision was still preserved here to permit the recognition of movement, and it probably could have been charted, and all other vision of this eye had disappeared. It would have permitted the conclusion, even if Dr. Evans's statement had not been obtained, that vision in the left eye probably failed first in the temporal field, and would indicate that the pressure came first on the inner fibers of the right optic tract or inner fibers of the left optic nerve. By discovering the recognition of motion in the nasal field

when all other vision in an eye seems to be lost, except perhaps that for light, we have a sign of value in suspected tumor of the pituitary gland. The sign may be of value when other signs of pituitary tumor are not conclusive.

The case to which I have just made reference shows that the field for motion exists independently of the other fields of form, light, color, in lesions of the optic tracts or chiasm as well as in lesions of the occipital lobe, but probably recognition of light is necessary for the proper recognition of motion. It shows that motion is probably the last form of vision to disappear, and is important in connection with Riddoch's statement that appreciation of movement returns before the object as such is recognized. His statement that light and movement are probably the most primitive of all visual percepts, and consequently they would be perceived first in a recovering blind field, explains also why motion is the last form of vision to disappear. Recognition of movement, as he says, is essential to animals both for hunting and for self-preservation; thus naturally it would have a wide field.

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### CONGENITAL DEXTROCARDIA.

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ANOMALIES of the heart, partly because of their infrequent occurrence and partly because of their occult manifestations, are of particular interest to the clinician. I have recently been afforded the opportunity of observing three cases of congenital dextrocardia. Two types of this anomaly are recognized: one associated with transposition of the abdominal viscera (*situs transversus*), and the other, in which the transposition affects only the heart and great vessels. At times<sup>3</sup> anomalous arrangement of the venæ cavæ permits the admixture of arterial and venous blood; this gives rise to a clinical picture simulating the syndrome of congenital heart disease.

Recalling the embryological development of the heart, it is readily seen how transposition of this organ occurs. The two primitive cardiac tubes fuse into one about the fifteenth day<sup>2</sup> and an auricular, ventricular and bulbar subdivision becomes evident (Fig. 1). The tube soon becomes bent on itself, which determines largely the future axis of the heart. In congenital transposition the primitive tube bends into a contrasigmoid (S) instead of the normal sigmoid (S) manner. This has been explained<sup>1</sup> by assuming that the embryo lies in an abnormal position within the chorion, so that its right side instead of its left lies closer to the blood supply. The three

patients whom I examined presented the most frequent anomaly, dextrocardia with *situs transversus*. In no instance was there any complaint referable to the abnormality.

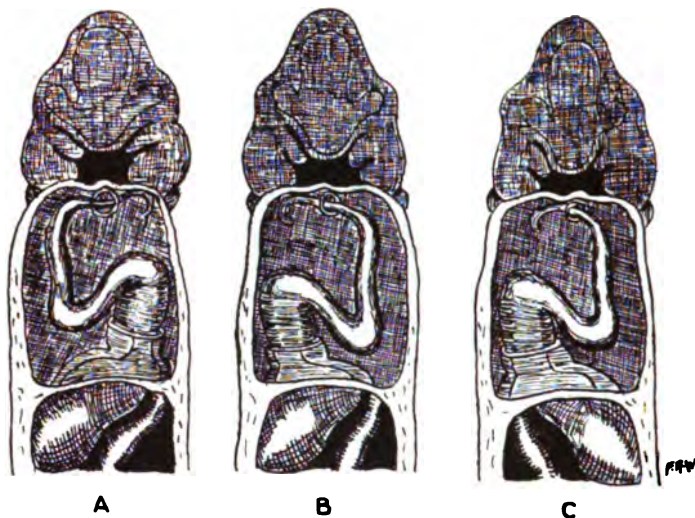


FIG. 1.—Transposition of the viscera in the embryo. A, normal; B, simple dextrocardia; C, complete situs transversus. Human embryo of about fifteen days. (After His.)

#### REPORT OF CASES.

CASE I (222329).—A woman, aged forty years, presented herself for examination complaining of chest pains of the intercostal

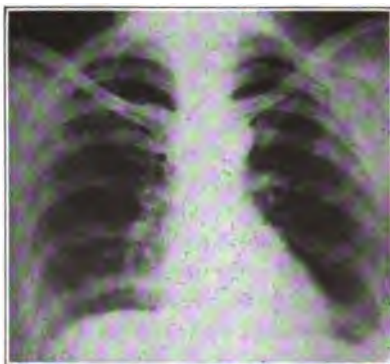


FIG. 2

neuralgic type. The apex-beat of the heart was palpable in the fifth right intercostal space 7.5 cm. from the midsternal line. The cardiac dulness extended 9.0 cm. to the right and 1.5 cm. to the left

of the midsternum. The heart sounds were best heard at the apex. Liver dulness was found to be on the left side and gastric tympany on the right. The systolic blood-pressure was 152, the diastolic was 90. Radiograms of the chest showed the dextrocardia and a trans-



FIG. 3

position of the stomach and colon (fluoroscopic colon). The electrocardiogram showed the heart-rate to be 94. Complete inversion of Leads I and II. The amplitude of the *R* waves in Leads I and II exceeded those in Lead III by one-third (Figs. 2, 3 and 4).

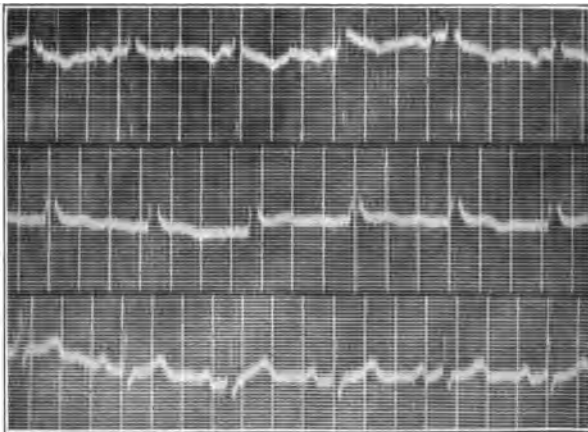


FIG. 4

**CASE II (224506).**—A woman, aged thirty-seven years, presented herself for examination on account of a pelvic complaint. The apex-beat of the heart was palpable in the sixth right intercostal space,



FIG. 5



FIG. 6

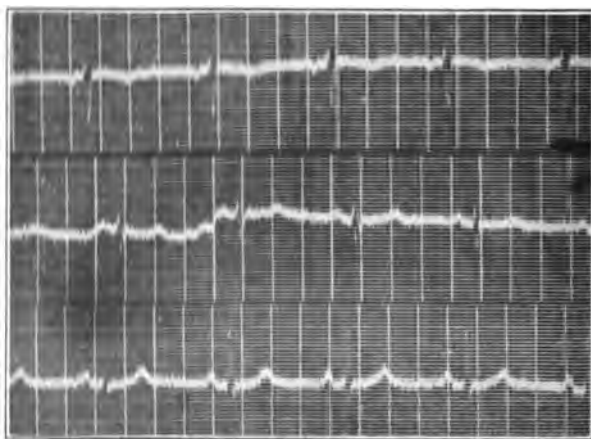


FIG. 7

9.0 cm. from the midsternal line. The cardiac dulness extended 11.0 cm. to the right of the midsternum. The heart sounds were best heard at the apex. Liver dulness was found on the left side and gastric tympany on the right. A bilateral salpingitis and a cyst of the left ovary were palpated. The systolic blood-pressure was 120, the diastolic was 75. The radiograms revealed dextrocardia and transposition of the stomach and colon (fluoroscopic colon). The electrocardiogram showed the heart-rate to be 75. There was complete inversion of Lead I. The amplitude of the *R* waves in Lead I were practically the same as those in Lead II and exceeded those in Lead III by slightly more than a third (Figs. 5, 6 and 7).



FIG. 8

**CASE III (238633).**—A woman, aged thirty-three years, presented herself for examination on account of goitre. The heart, as in the other cases, was found to be on the right side. The liver dulness was found on the left side and the gastric tympany on the right. The patient had a single adenoma of the right lobe of the thyroid 4.0 by 4.5 cm. The systolic blood-pressure was 112, the diastolic was 78. The radiogram revealed dextrocardia and transposition of the colon. The electrocardiogram showed the heart-rate to be 115; there was complete inversion of Lead I, and the amplitude of the *R* waves in Lead I were diminished to about one-half those of Lead III. The amplitude of the *R* waves in Lead III slightly exceeded those in Lead II. There was evidence of left ventricular preponderance (Figs. 8, 9 and 10).

The electrocardiograms of the last two cases essentially confirm the findings recorded in previous publications.<sup>4 5 7 8</sup> Lead I shows a complete inversion of all the deflections. Fig. 11 illustrates the angles produced by the direction of the leads and the resulting electrocardiograms. Case I (222329) shows the inversion also involving Lead II, and is explained by an exaggeration of the incli-

nation of the cardiac axis to the right. The leads represent fixed planes of electrical potential, and changes in cardiac position or alterations in muscle bulk preponderance obviously affect the electrical currents, as expressed by the electrocardiograms.



FIG. 9

It has been mentioned<sup>6</sup> that the *R* wave in Lead III becomes taller than in Lead II, but in these reported cases no constancy was

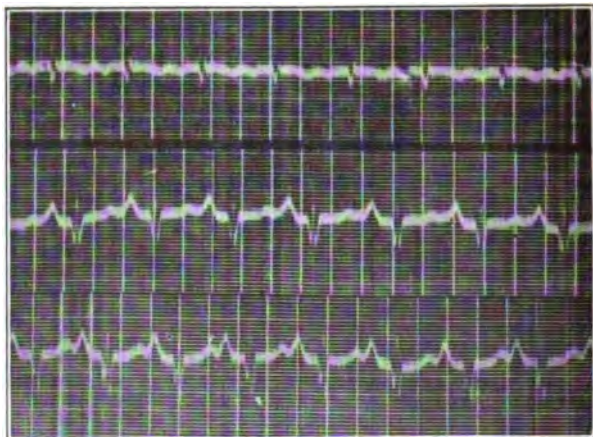


FIG. 10

observed. Hirschfelder mentions that the electrocardiographic curves sometimes are practically normal. Inversion of the deflections in Lead I is definite evidence of congenital dextrocardia with



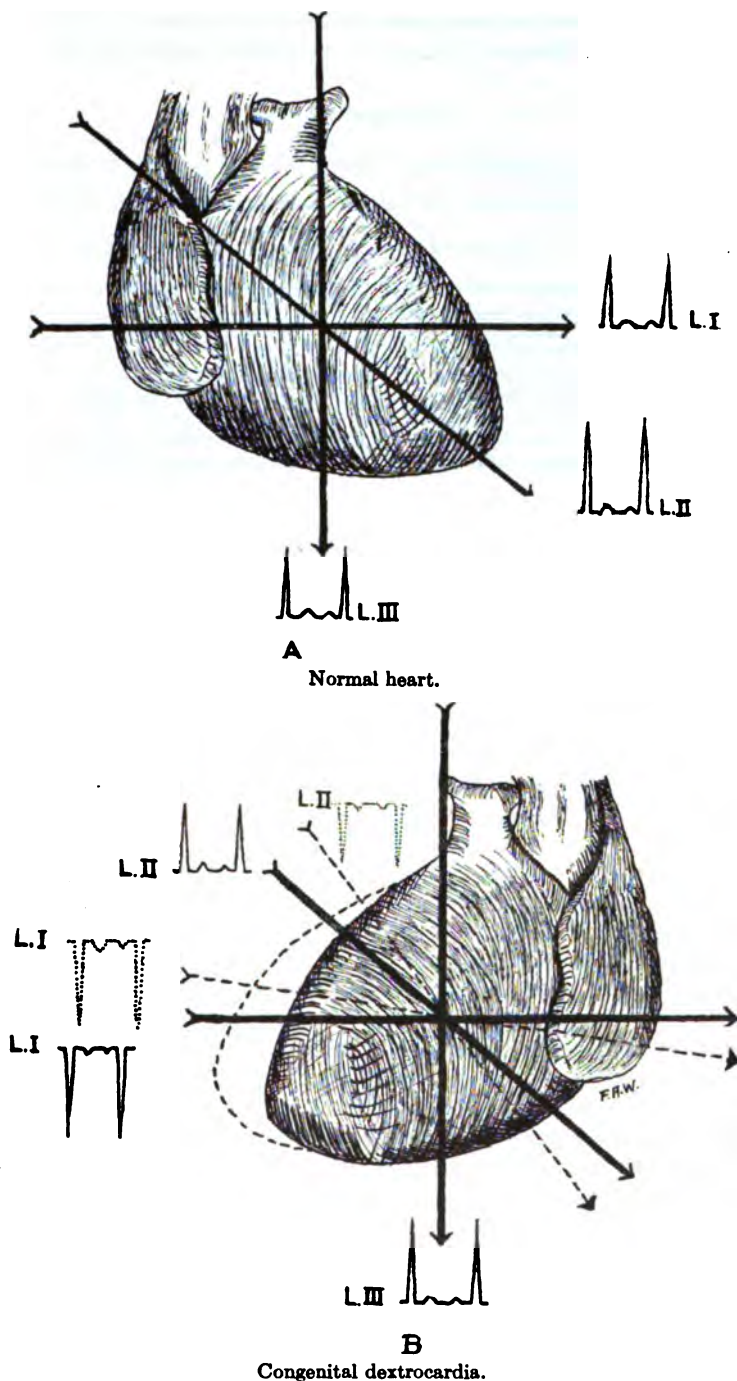


FIG. 11.—Schematic representations showing the angles produced by the direction of the leads and the resulting electrocardiograms. The dotted lines in Fig. B show the inclination to the right exaggerated and the inversion affecting Lead II.

*situs transversus*, and we recognize electrocardiography as a valuable adjunct in the differential diagnosis of cardiac displacements.

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### PROTOZOAL INFECTIONS OF THE INTESTINES:

WITH EMPHASIS ON THEIR INCIDENCE AND BEHAVIOR IN OTHER  
THAN TROPICAL REGIONS AND ON THE PATHOGENICITY AND  
TREATMENT OF CERTAIN OF THE FLAGELLATES.

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AND

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IN war time the environment of every military camp is menaced by the diseases that become epidemic among the troops.

That protozoal infections are not confined to the tropics we are having abundant evidence from the reported cases and studies by men in every part of the country. These parasites are of special interest at present on account of the movement of carriers, due to war activities, with the infection of new regions and new contacts. In the Philippines and in the Canal Zone amebic dysentery was one of the foremost foes of white men, soldiers or civilians. Sanitation and preventive medicine are doing much to stop the spread of this and of other protozoal infections, but they must still be looked upon as dangers to camp life and to the adjacent communities.

This is particularly true now that we know of the existence of carriers who need never have visited in Southern countries and in whom the infection seldom declares itself in a frank dysentery, so that they go about for years improperly treated unless their physician is exceptionally thorough in his investigations.

The indications for fecal study were outlined by Sistrunk<sup>1</sup> in his paper, one of the early reports of so-called tropical infections occurring in residents of other regions. The stools of 110 patients with either chronic diarrhea, the passage of blood and mucus, anemia or obscure abdominal symptoms were examined. Of these, 65 had intestinal protozoa, chiefly amebas or trichomonas.

Smithies<sup>2</sup> reported in July, 1917, the study of the stools of 1000 patients at Augustana Hospital, in which series 98, or 9.8 per cent., showed intestinal protozoa either ameba or one of the flagellates. This report with others has undoubtedly quickened our interest in the subject and made us keener in searching for and recognizing the protozoa even though occurring far from the tropics. Practically all of Dr. Smithies' cases came from the northern half of the Central States. It is worthy of note that in most of his cases two or more varieties of protozoa were found in the stools.

It may not be out of place here briefly to summarize our knowledge of the habits of the parasitic protozoa and the principles governing their control.

Entamebic dysentery is caused by a distinct species of ameba (*ameba histolytica*), an obligatory parasite, whose host, so far as is known definitely, is man. The disease can reach the intestine of man only by the ingestion of material containing *Entameba histolytica*, generally in the encysted stage. These ameba may originate from acute cases or, more commonly, from convalescent carriers, or even from individuals who have never had dysentery, but are contact carriers. Such apparently healthy carriers on account of the cysts in their stools are more dangerous than the patient in the acute stage of the disease.

The flagellates (*cercomonas*, *trichomonas*, *tetramitus*) have not until recently been generally regarded as pathogenic. For this reason they have not been so thoroughly studied nor have means to combat them been so much searched for. In Panama the chief interest they called forth was the frequency with which they were associated with ameba, demanding more careful search for the latter. *Trichomonas*, the one most commonly found, does not form cysts so far as known, the so-called cysts being *blastocystis hominis*.

In regard to the flagellates, Brumpt<sup>3</sup> says that diarrheal conditions have been attributed to them when present in large numbers. A certain amount of irritation is necessary for their development, but once started, their multiplication may keep up a chronic intestinal catarrh. In the Andaman Islands, Anderson found *trichomonas* 723 times in 920 cases of dysentery, associated with ameba in 459 cases; flagellates were rare in 210 non-dysentery patients. Brumpt

<sup>1</sup> Jour. Am. Med. Assn., November 4, 1911, No. 19, lvii, 1507.

<sup>2</sup> Medicine and Surgery, July, 1917, p. 460.

<sup>3</sup> Parasitologie, Paris, 1913.

says that patients with monads almost always have a low or absent stomach acidity.

The attitude of the military surgeon to the protozoa is largely one of prophylaxis. Once having gained entrance to a camp, they tend rapidly to become epidemic and threaten to incapacitate large numbers of men. Such conditions call for the most intelligent and vigorous prophylactic measures, as shown by our experience in the Philippines, the Canal Zone and on the Mexican border.

The attitude of the civilian physician to the sporadic cases he meets is more one of the therapeutic handling of the individual case, although the protection of those about the patient ought not to be overlooked simply because it presents comparatively little difficulty.

The question of prophylaxis is essentially that in typhoid fever. The details of these prophylactic measures are so thoroughly standardized that we shall not enter into their discussion. As to the specific destruction of the intruder there is still much variation of opinion and the therapeutic treatment continues to tax the best efforts of clinicians. One after another, specific methods of treatment have been proclaimed as successful, only to give place later to a new method boasting a higher percentage of cures. Just what constitutes a permanent cure seems still a vexed question with certain authors. May not the difference in susceptibility of protozoa to chemicals, shown by Brem and Zeiler<sup>4</sup> in experimenting on ameba with quinin, and as suggested by them in reference to ipecac, determine to some extent the time demanded for permanent cure, as well as the selection of the chemical for the individual case?

A few facts related to treatment stand forth as apparently proved. Ipecac in some form seems to have a distinctly beneficial effect upon the symptoms and plays at least a part in practically all methods of treatment directed against the ameba, although upon the flagellates it seems to exert only temporary influence. It would seem that in the attack upon the ameba it is necessary to place the drug both in the blood stream and on the intestinal lining, although some clinicians (Manson, Dock, Niles and Simon) claim satisfactory results from the use of large doses of the powdered drug placed below the stomach by means of properly protected pills, a good description of which is given by Niles.<sup>5</sup> Others use the alkaloid emetin placed into the circulation by needle, sometimes supplemented by arsenic subcutaneously or intravenously. The advocates of both of these methods claim good results and see no need of colonic irrigations as an aid to the specific treatment.

It seems to be becoming more and more popular to attack every known or suspected protozoal infection, from pox to pellagra, by pumping arsenic into the circulation. We are, however, impressed with the results claimed by certain observers from the combined use

<sup>4</sup> AM. JOUR. MED. SC., November, 1910, p. 669.

<sup>5</sup> Ibid., October, 1914, p. 526.

of emetin hypodermically and salvarsan intravenously. The use of arsphenamin and neosarsphenamin has been extended to the amebic infections by Wynne,<sup>6</sup> and is now established as a definite treatment when used in connection with emetin. The recent paper by Dr. Herbert Gunn<sup>7</sup> at the meeting of the California State Medical Society is a valuable contribution to the treatment of carriers.

While touching briefly on treatment we cannot resist calling attention to the importance of detecting and subjecting to treatment the carriers of the *Entameba histolytica*. They are doubly dangerous in any community up to the time that suspicion is directed toward them, after which a careful study of the stool promptly identifies them, and they are then fair targets for therapeutic attack. These carriers present the ameba in the encysted form, which apparently is impervious to ordinary attack. An agent interesting to clinicians in this connection is the emetin-bismuth-iodide, which by some recent observers has seemed to be at least fairly satisfactory against encysted ameba. It is not claimed to have any appreciable effect upon flagellates. We feel also impelled to record the only method that with us has proved at all satisfactory in treating the flagellate *trichomonas intestinalis*, namely, the giving of large doses of calomel followed by saline purgation, once every four or five days, coupled with daily colonic irrigation of mercuric chloride (1 in 10,000 to 1 in 20,000). We are experimenting with other chemicals in the hope of finding something that will have a specific and permanent effect on them.

In a group of 46 cases coming under our notice during the past year, with symptoms seeming to demand a careful search for intestinal parasites, 19, or 41.3 per cent., showed protozoal parasites many times accompanied by other intruders. So frequently have the *trichomonas* presented, in association with troublesome and even grave symptoms, that we incline to agree with Freund,<sup>8</sup> who says: "I firmly believe that *trichomonas* is the direct cause of certain forms of acute, chronic and recurring enteritis, with abdominal pain, diarrhea, loss in weight, elevation of temperature and at times anemia." At the time (1908) when he made this statement he reported one case that died of progressive pernicious anemia and another less grave that recovered, although strongly suggesting the pernicious type of anemia.

While our group is too small to serve as a basis for statistical analysis, yet the suggested prevalence of these diseases in our community is worthy of attention. Also, the little group presents so many cases of striking individual interest, both as to course and treatment, that we have felt justified in discussing a few of them.

<sup>6</sup> Cited by James: Proc. Med. Assn., Canal Zone, vol. vi, part 1, p. 98.

<sup>7</sup> California State Jour Med., May, 1918, p. 240.

<sup>8</sup> Arch. Int. Med., 1908, No. 1, i, 28.

Hospital, December 31, 1918. She had been under the care of Dr. Edward R. Evans, of Utica, N. Y., who reported that he had found decided choked disks. Each day as he tested for hemianopsia it seemed that objects in the left temporal field were considerably less distinct than in the right field. Vision steadily diminished during two weeks, and when examined by Captain Cross advanced optic atrophy was found in the left eye and much atrophy also in the right eye, with many fresh hemorrhages which probably accounted for sudden loss of vision.

In examining her roughly with the hand, with a black object 6 x 4 inches, or a white hairbrush, I found that with her left eye she saw movement only in the nasal field but could not tell what the object was. She had no vision in the temporal field even for motion. With her right eye alone she recognized a large object in both nasal and temporal fields, but more distinctly in the nasal field. She recognized movement promptly in both nasal and temporal fields of her right eye.

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### CONGENITAL DEXTROCARDIA.

BY F. A. WILLIUS, M.D.,

MAYO CLINIC, ROCHESTER, MINNESOTA.

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patients whom I examined presented the most frequent anomaly, dextrocardia with *situs transversus*. In no instance was there any complaint referable to the abnormality.

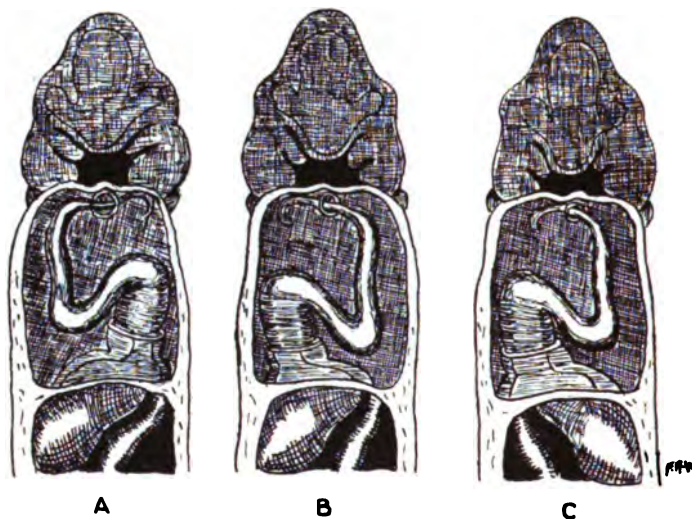


FIG. 1.—Transposition of the viscera in the embryo. A, normal; B, simple dextrocardia; C, complete situs transversus. Human embryo of about fifteen days. (After His.)

#### REPORT OF CASES.

CASE I (222329).—A woman, aged forty years, presented herself for examination complaining of chest pains of the intercostal



FIG. 2

neuralgic type. The apex-beat of the heart was palpable in the fifth right intercostal space 7.5 cm. from the midsternal line. The cardiac dulness extended 9.0 cm. to the right and 1.5 cm. to the left

of the midsternum. The heart sounds were best heard at the apex. Liver dulness was found to be on the left side and gastric tympany on the right. The systolic blood-pressure was 152, the diastolic was 90. Radiograms of the chest showed the dextrocardia and a trans-

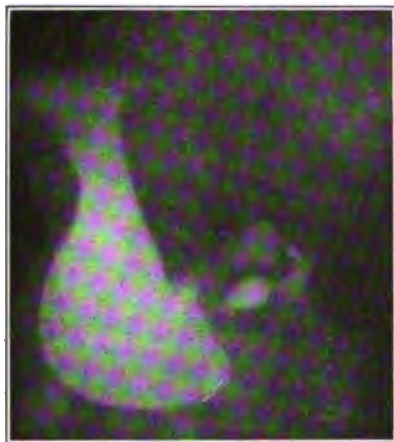


FIG. 3

position of the stomach and colon (fluoroscopic colon). The electrocardiogram showed the heart-rate to be 94. Complete inversion of Leads I and II. The amplitude of the *R* waves in Leads I and II exceeded those in Lead III by one-third (Figs. 2, 3 and 4).

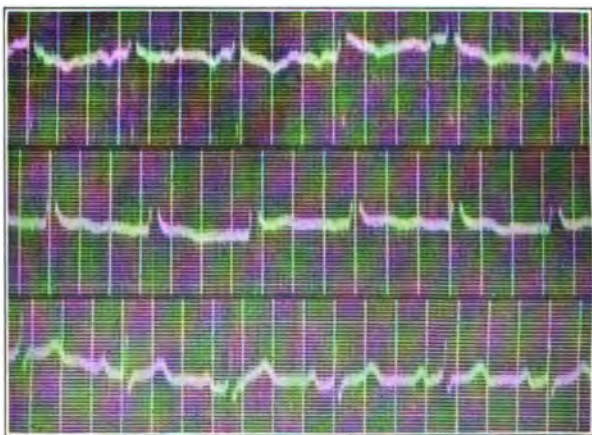


FIG. 4

**CASE II (224506).**—A woman, aged thirty-seven years, presented herself for examination on account of a pelvic complaint. The apex-beat of the heart was palpable in the sixth right intercostal space,

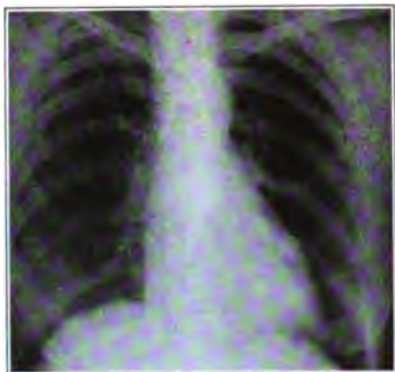


FIG. 5



FIG. 6

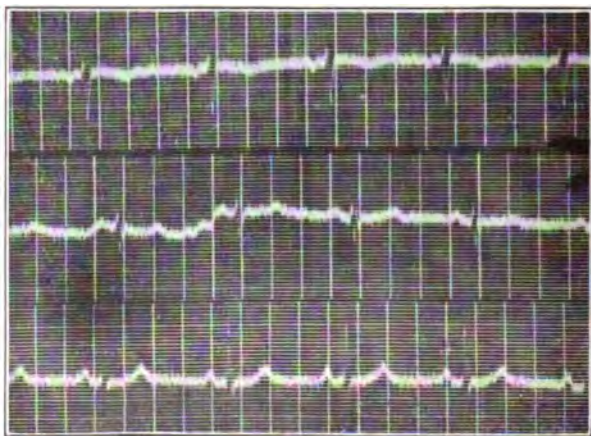


FIG. 7

9.0 cm. from the midsternal line. The cardiac dulness extended 11.0 cm. to the right of the midsternum. The heart sounds were best heard at the apex. Liver dulness was found on the left side and gastric tympany on the right. A bilateral salpingitis and a cyst of the left ovary were palpated. The systolic blood-pressure was 120, the diastolic was 75. The radiograms revealed dextrocardia and transposition of the stomach and colon (fluoroscopic colon). The electrocardiogram showed the heart-rate to be 75. There was complete inversion of Lead I. The amplitude of the *R* waves in Lead I were practically the same as those in Lead II and exceeded those in Lead III by slightly more than a third (Figs. 5, 6 and 7).



FIG. 8

CASE III (238633).—A woman, aged thirty-three years, presented herself for examination on account of goitre. The heart, as in the other cases, was found to be on the right side. The liver dulness was found on the left side and the gastric tympany on the right. The patient had a single adenoma of the right lobe of the thyroid 4.0 by 4.5 cm. The systolic blood-pressure was 112, the diastolic was 78. The radiogram revealed dextrocardia and transposition of the colon. The electrocardiogram showed the heart-rate to be 115; there was complete inversion of Lead I, and the amplitude of the *R* waves in Lead I were diminished to about one-half those of Lead III. The amplitude of the *R* waves in Lead III slightly exceeded those in Lead II. There was evidence of left ventricular preponderance (Figs. 8, 9 and 10).

The electrocardiograms of the last two cases essentially confirm the findings recorded in previous publications.<sup>4 5 7 8</sup> Lead I shows a complete inversion of all the deflections. Fig. 11 illustrates the angles produced by the direction of the leads and the resulting electrocardiograms. Case I (222329) shows the inversion also involving Lead II, and is explained by an exaggeration of the incli-

nation of the cardiac axis to the right. The leads represent fixed planes of electrical potential, and changes in cardiac position or alterations in muscle bulk preponderance obviously affect the electrical currents, as expressed by the electrocardiograms.



FIG. 9

It has been mentioned<sup>6</sup> that the *R* wave in Lead III becomes taller than in Lead II, but in these reported cases no constancy was

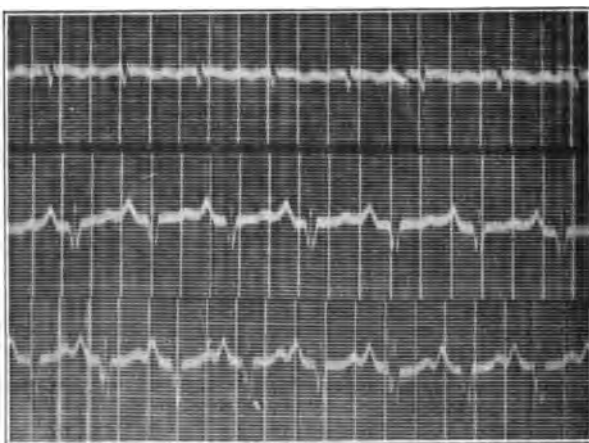


FIG. 10

observed. Hirschfelder mentions that the electrocardiographic curves sometimes are practically normal. Inversion of the deflections in Lead I is definite evidence of congenital dextrocardia with

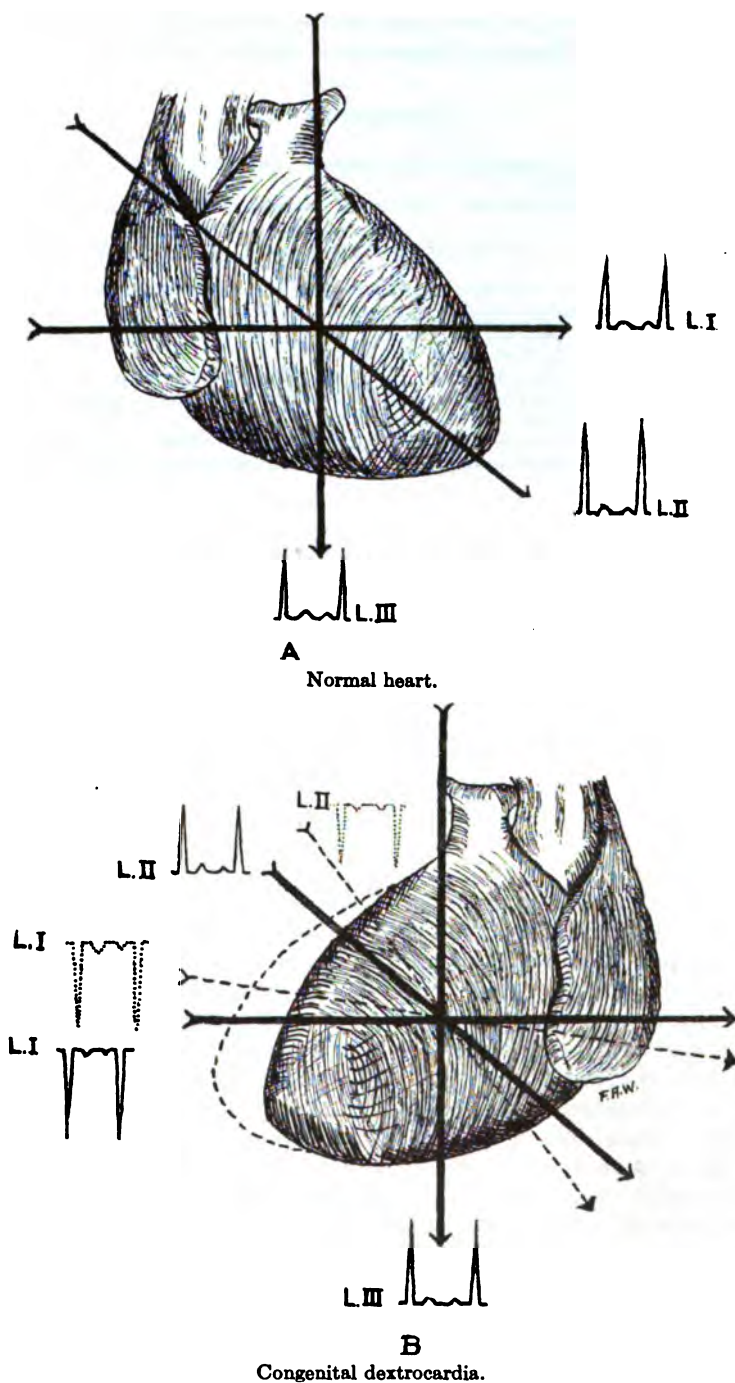


FIG. 11.—Schematic representations showing the angles produced by the direction of the leads and the resulting electrocardiograms. The dotted lines in Fig. B show the inclination to the right exaggerated and the inversion affecting Lead II.



*situs transversus*, and we recognize electrocardiography as a valuable adjunct in the differential diagnosis of cardiac displacements.

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### PROTOZOAL INFECTIONS OF THE INTESTINES:

WITH EMPHASIS ON THEIR INCIDENCE AND BEHAVIOR IN OTHER  
THAN TROPICAL REGIONS AND ON THE PATHOGENICITY AND  
TREATMENT OF CERTAIN OF THE FLAGELLATES.

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AND

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IN war time the environment of every military camp is menaced by the diseases that become epidemic among the troops.

That protozoal infections are not confined to the tropics we are having abundant evidence from the reported cases and studies by men in every part of the country. These parasites are of special interest at present on account of the movement of carriers, due to war activities, with the infection of new regions and new contacts. In the Philippines and in the Canal Zone amebic dysentery was one of the foremost foes of white men, soldiers or civilians. Sanitation and preventive medicine are doing much to stop the spread of this and of other protozoal infections, but they must still be looked upon as dangers to camp life and to the adjacent communities.

This is particularly true now that we know of the existence of carriers who need never have visited in Southern countries and in whom the infection seldom declares itself in a frank dysentery, so that they go about for years improperly treated unless their physician is exceptionally thorough in his investigations.



The indications for fecal study were outlined by Sistrunk<sup>1</sup> in his paper, one of the early reports of so-called tropical infections occurring in residents of other regions. The stools of 110 patients with either chronic diarrhea, the passage of blood and mucus, anemia or obscure abdominal symptoms were examined. Of these, 65 had intestinal protozoa, chiefly amebas or trichomonas.

Smithies<sup>2</sup> reported in July, 1917, the study of the stools of 1000 patients at Augustana Hospital, in which series 98, or 9.8 per cent., showed intestinal protozoa either ameba or one of the flagellates. This report with others has undoubtedly quickened our interest in the subject and made us keener in searching for and recognizing the protozoa even though occurring far from the tropics. Practically all of Dr. Smithies' cases came from the northern half of the Central States. It is worthy of note that in most of his cases two or more varieties of protozoa were found in the stools.

It may not be out of place here briefly to summarize our knowledge of the habits of the parasitic protozoa and the principles governing their control.

Entamebic dysentery is caused by a distinct species of ameba (*ameba histolytica*), an obligatory parasite, whose host, so far as is known definitely, is man. The disease can reach the intestine of man only by the ingestion of material containing *Entameba histolytica*, generally in the encysted stage. These ameba may originate from acute cases or, more commonly, from convalescent carriers, or even from individuals who have never had dysentery, but are contact carriers. Such apparently healthy carriers on account of the cysts in their stools are more dangerous than the patient in the acute stage of the disease.

The flagellates (*cercomonas*, *trichomonas*, *tetramitus*) have not until recently been generally regarded as pathogenic. For this reason they have not been so thoroughly studied nor have means to combat them been so much searched for. In Panama the chief interest they called forth was the frequency with which they were associated with ameba, demanding more careful search for the latter. *Trichomonas*, the one most commonly found, does not form cysts so far as known, the so-called cysts being *blastocystis hominis*.

In regard to the flagellates, Brumpt<sup>3</sup> says that diarrheal conditions have been attributed to them when present in large numbers. A certain amount of irritation is necessary for their development, but once started, their multiplication may keep up a chronic intestinal catarrh. In the Andaman Islands, Anderson found *trichomonas* 723 times in 920 cases of dysentery, associated with ameba in 459 cases; flagellates were rare in 210 non-dysentery patients. Brumpt

<sup>1</sup> Jour. Am. Med. Assn., November 4, 1911, No. 19, lvii, 1507.

<sup>2</sup> Medicine and Surgery, July, 1917, p. 460.

<sup>3</sup> Parasitologie, Paris, 1913.

says that patients with monads almost always have a low or absent stomach acidity.

The attitude of the military surgeon to the protozoa is largely one of prophylaxis. Once having gained entrance to a camp, they tend rapidly to become epidemic and threaten to incapacitate large numbers of men. Such conditions call for the most intelligent and vigorous prophylactic measures, as shown by our experience in the Philippines, the Canal Zone and on the Mexican border.

The attitude of the civilian physician to the sporadic cases he meets is more one of the therapeutic handling of the individual case, although the protection of those about the patient ought not to be overlooked simply because it presents comparatively little difficulty.

The question of prophylaxis is essentially that in typhoid fever. The details of these prophylactic measures are so thoroughly standardized that we shall not enter into their discussion. As to the specific destruction of the intruder there is still much variation of opinion and the therapeutic treatment continues to tax the best efforts of clinicians. One after another, specific methods of treatment have been proclaimed as successful, only to give place later to a new method boasting a higher percentage of cures. Just what constitutes a permanent cure seems still a vexed question with certain authors. May not the difference in susceptibility of protozoa to chemicals, shown by Brem and Zeiler<sup>4</sup> in experimenting on ameba with quinin, and as suggested by them in reference to ipecac, determine to some extent the time demanded for permanent cure, as well as the selection of the chemical for the individual case?

A few facts related to treatment stand forth as apparently proved. Ipecac in some form seems to have a distinctly beneficial effect upon the symptoms and plays at least a part in practically all methods of treatment directed against the ameba, although upon the flagellates it seems to exert only temporary influence. It would seem that in the attack upon the ameba it is necessary to place the drug both in the blood stream and on the intestinal lining, although some clinicians (Manson, Dock, Niles and Simon) claim satisfactory results from the use of large doses of the powdered drug placed below the stomach by means of properly protected pills, a good description of which is given by Niles.<sup>5</sup> Others use the alkaloid emetin placed into the circulation by needle, sometimes supplemented by arsenic subcutaneously or intravenously. The advocates of both of these methods claim good results and see no need of colonic irrigations as an aid to the specific treatment.

It seems to be becoming more and more popular to attack every known or suspected protozoal infection, from pox to pellagra, by pumping arsenic into the circulation. We are, however, impressed with the results claimed by certain observers from the combined use

<sup>4</sup> AM. JOUR. MED. SC., November, 1910, p. 669.

<sup>5</sup> Ibid., October, 1914, p. 526.

of emetin hypodermically and salvarsan intravenously. The use of arsphenamin and neosarsphenamin has been extended to the amebic infections by Wynne,<sup>6</sup> and is now established as a definite treatment when used in connection with emetin. The recent paper by Dr. Herbert Gunn<sup>7</sup> at the meeting of the California State Medical Society is a valuable contribution to the treatment of carriers.

While touching briefly on treatment we cannot resist calling attention to the importance of detecting and subjecting to treatment the carriers of the *Entameba histolytica*. They are doubly dangerous in any community up to the time that suspicion is directed toward them, after which a careful study of the stool promptly identifies them, and they are then fair targets for therapeutic attack. These carriers present the ameba in the encysted form, which apparently is impervious to ordinary attack. An agent interesting to clinicians in this connection is the emetin-bismuth-iodide, which by some recent observers has seemed to be at least fairly satisfactory against encysted ameba. It is not claimed to have any appreciable effect upon flagellates. We feel also impelled to record the only method that with us has proved at all satisfactory in treating the flagellate *trichomonas intestinalis*, namely, the giving of large doses of calomel followed by saline purgation, once every four or five days, coupled with daily colonic irrigation of mercuric chloride (1 in 10,000 to 1 in 20,000). We are experimenting with other chemicals in the hope of finding something that will have a specific and permanent effect on them.

In a group of 46 cases coming under our notice during the past year, with symptoms seeming to demand a careful search for intestinal parasites, 19, or 41.3 per cent., showed protozoal parasites many times accompanied by other intruders. So frequently have the *trichomonas* presented, in association with troublesome and even grave symptoms, that we incline to agree with Freund,<sup>8</sup> who says: "I firmly believe that *trichomonas* is the direct cause of certain forms of acute, chronic and recurring enteritis, with abdominal pain, diarrhea, loss in weight, elevation of temperature and at times anemia." At the time (1908) when he made this statement he reported one case that died of progressive pernicious anemia and another less grave that recovered, although strongly suggesting the pernicious type of anemia.

While our group is too small to serve as a basis for statistical analysis, yet the suggested prevalence of these diseases in our community is worthy of attention. Also, the little group presents so many cases of striking individual interest, both as to course and treatment, that we have felt justified in discussing a few of them.

<sup>6</sup> Cited by James: Proc. Med. Assn., Canal Zone, vol. vi, part 1, p. 98.

<sup>7</sup> California State Jour Med., May, 1918, p. 240.

<sup>8</sup> Arch. Int. Med., 1908, No. 1, i, 28.

CASE I.—A mining engineer, aged thirty-six years, contracted amebic infection in Colombia and had been cured and had relapsed several times before coming under our notice. He was emaciated, anemic and running a temperature ranging from 99° to 102°. He was sensitive to pressure throughout the entire abdomen and had griping pain when the bowel moved. The stools were frequent and liquid, containing mucus, pus and blood, and showed under the microscope myriads of *Ameba histolytica*. This case presented the clinical picture of a severe amebic infection. The outlook was not promising and the progress at first was discouraging. However, with absolute rest in bed and careful attention to diet and nursing, he made a good recovery in about three months. He returned to the city about six months later, with a distinct relapse to all of his old symptoms, although they were not so severe. He was again treated much as before, with similar results, and after nine months has not again relapsed. This case we feel illustrates a not uncommon course of severe amebic infection treated in the most generally accepted manner, with emetin injections, ipecac by mouth and colonic saline irrigation. He relapsed because the encysted ameba were not all destroyed, and meanwhile he was a convalescent carrier of constant menace to those about him.

Case No.	Reported in detail.	Sex.	Age.	Place of original infection.	Clinical symptoms.	Protozoa.
1	r	M.	26	South America	Dysentery	<i>Ameba histolytica</i> .
2	r	M.	23	Mexico	Dysentery	<i>Ameba histolytica</i> .
3	r	M.	43	South America	Hyperchlorhydria	<i>Ameba histolytica</i> ; oxyurias; bothriocephalus; round-worm.
4	..	F.	35	United States	Dysentery	<i>Ameba histolytica</i> ; trichomonas.
5	..	M.	65	.....	Achylia; diarrhea	Trichomonas.
6	r	M.	47	Philippines	Nervous exhaustion; hypochlorhydria	<i>Ameba histolytica</i> ; trichomonas.
7	r	F.	43	Minnesota	Diarrhea; hyperchlorhydria	Trichomonas.
8	r	F.	47	Mexico	Fever; chills	Trichomonas.
9	..	F.	46	.....	.....	Trichomonas.
10	r	M.	68	Wisconsin	Anemia (pernicious?)	<i>Ameba histolytica</i> ; trichocephalus.
11	r	M.	38	Mid-West	Intermittent diarrhea	<i>Ameba histolytica</i> ; trichomonas.
12	..	M.	50	South Africa	Intestinal indigestion; constipation	<i>Ameba histolytica</i> .
13	..	M.	59	Mexico	Dysentery	<i>Ameba histolytica</i> ; uncinaria; strongyloids.
14	..	M.	58	New Jersey	Dysentery	<i>Ameba histolytica</i> .
15	..	M.	40	North Carolina	Dysentery	<i>Ameba histolytica</i> .
16	..	F.	40	Nebraska	Constipation	<i>Ameba histolytica</i> and monads.
17	r	M.	37	Cuba	Attacks of somnolence	<i>Ameba histolytica</i> ; trichomonas.
18	..	F.	65	Japan	Diarrhea; achylia	<i>Ameba histolytica</i> .
19	r	M.	43	Northern U. S.	Diarrhea	Trichomonas.

\* r = reported at length in body of paper.

CASE II.—Male, Spaniard, aged twenty-three years, who had lived in Mexico, presented typical symptoms of acute amebic dysentery; acquired complete relief of symptoms under intravenous injections of emetin and kerosene enemata. Like Case I, the cysts persisted in the stools and were so recorded when he returned to Mexico against our advice.

CASE III.—A mining prospector, aged forty-three years, who had suffered severe malaria, with intestinal hemorrhages, while in Colombia, on his return to California sought relief for definite hyperchlorhydria symptoms. The blood examination, while showing no anemia, directed our attention to the bowel by a 7 per cent. eosinophilia. The stools on examination showed pin-worms, many ova of *Bothriocephalus latus*, an unknown species of round-worm and numerous *Ameba histolytica*. This man has had no dysentery since his malaria, and after his hyperchlorhydria was corrected by proper diet, he expressed himself as feeling well, and shortly afterward disappeared. He had been cleaned out with calomel and santonin and given a course of alcresta ipecac, with what permanent results we are unable to report. The case is quoted to illustrate the effect of intestinal intruders upon the blood and stomach glands as well as to show that a strong adult can carry about quite a lively fauna, with none of their characteristic symptoms in evidence.

CASE VI.—An army officer, aged forty-seven years, who had seen service in the Philippines, suffering both severe malaria and yellow fever, but not dysentery. Repeated stool examinations during the previous year had always shown *trichomonas intestinalis hominis*. He was nervous and generally run down, with a slight degree of anemia and a lowered gastric chemistry. The bowel was for the most part slightly constipated; abundant monads were found in the stools. He was persuaded to start his furlough with several weeks' rest and upbuilding treatment. Although ameba later showed in the stools, he markedly gained in every way, and is now at the end of a year actively engaged on the Western front. We were unable to learn how completely the protozoa were eliminated from the stools at the army hospital where he was later treated, but we feel that his transference to Northern latitudes would have a tendency to reduce their virulence. This case suggests the possibility of overlooking the ameba even when attention is directed to the stools by the presence of other parasites.

CASE VII.—An unmarried woman, aged forty-three years, teacher and housekeeper, from Minnesota, never had been in a tropical latitude. Complained of hyperchlorhydria symptoms and tendency to diarrhea for many years. The hyperchlorhydria was demonstrated by analysis, with some pylorospasm and a ptosed stomach. The stools contained monads but no ameba. Careful roentgen-ray study showed no evidence of ulcer. Her stomach symptoms gradually improved under proper diet and support of that

viscus. Under this treatment and intermittent courses of colonic flushings a normal physiological bowel function was established without any tendency to loose stools. We are inclined to look upon this case as one of chronic diarrhea, due to monad irritation.

CASE VIII.—A somewhat analogous case was an unmarried woman, aged forty-seven years. She had never been of robust physique, although in no sense an invalid. For the past ten years, dating from a visit to Southern New Mexico, she had presented occasional fever paroxysms, much like a malarial seizure, with marked chill followed by  $1^{\circ}$  to  $4^{\circ}$  of fever and marked sweating. This complete cycle would be repeated daily for three to five days and gradually disappear. A blood examination made during a chill showed a leukocytosis of 17,000, with a straight polynuclear advance to 95 per cent. No malarial plasmodia could be demonstrated at any of several blood examinations. Slight evidence of colitis, without any bowel looseness, directed attention to the stools, which proved on examination to be swarming with monads. In this case the monads could be made to disappear from the stools by the free use of calomel by mouth and mercuric chloride (1 to 20,000) flushings of the colon. After some months of observation we found that if the monads were allowed to return to the stools the patient would promptly suffer a return of her paroxysms, which were absent as long as the stools were monad-free. This patient is still under observation. Her stomach chemistry was that of a moderate hypochlorhydria, with a tendency to constipation. Methylene blue and thymol were tried without success in this case.

CASE X.—An American business man, still active at sixty-eight, a year ago applied for relief from obstinate diarrhea. He showed complete absence of HCl and ferments in the gastric juice, and his diarrhea for a time was relieved by suitable diet and the free use of dilute HCl. A few months later he became quite anemic and dyspneic and his bowel began to trouble him again. The blood showed a marked secondary anemia, obscurely close to pernicious in type, the red cells falling to 1,500,000, and with the color index constantly 1.5. The stool showed abundant *Ameba histolytica* and trichomonas. The kidneys and other organs except the stomach were negative. By keeping him at rest and controlling his diet this patient's blood was gradually built up to normal in about three months, cacodylate of iron being used liberally in deep gluteal injections. This may have helped in the fight against the ameba, although both emetin hydrochloride and ipecac in pill form were persistently used. In this case we are inclined to attribute the final disappearance of the ameba to the free use of salol-coated pills of powdered ipecac. A few monads have persisted in this case, more, we feel, because of the patient's refusal to be "fussed" with when once he felt well again. This man had never been in the tropics.

CASE XI.—An energetic American business man, aged thirty-eight years, complained of having had intermittent diarrhea most of his life, as had his father before him. He came from one of the Northern Middle West States and had never been out of the United States. His mild stomach symptoms were the expression of a moderate hypochlorhydria. The stools showed both *Ameba histolytica* and *trichomonas* in abundance. As he refused to rest he was treated throughout as an ambulatory case. He presented but little anemia and was in fair flesh and strength. Hypodermics of emetin followed by "Al Cresta" tablets cleared up the ameba, which were presumably not a very virulent strain. The monads also cleared up under the mercury treatment previously mentioned. Most of the monads we have met seemed to thrive in solution of methylene blue. At last reports about two months ago this case was apparently well. When compared with Case I it suggests the variability of virulence of these protozoa.

CASE XVII.—An American male, aged thirty-seven years, who had seen military service in Cuba and suffered from an epidemic of ileocolitis while encamped in Florida. He complained chiefly of having had for eighteen years lethargy, during attacks of which he would practically fall asleep while going about. The attacks would come on while working, riding horseback, talking, etc., and were fought off with great difficulty. *Ameba histolytica* and *trichomonas* were found in the stools. His somnolent attacks cleared up under emetin. Mild attacks recurred after three months and emetin was resorted to again and controlled the recurrence of his lethargic feeling. Two or three doses of the drug usually suffice for this purpose.

CASE XIX.—An American business man, aged forty-three years, who gave a history of recurring diarrheas extending over several years, attendant upon a general nervous breakdown. He had multiple diverticulitis, with general peritonitis and repeated abdominal abscesses. This case ran a long tedious course of abdominal trouble, with several operations to drain abscesses. As monads were early noticed in the stools we cannot resist speculating as to their possible role in the production of his trouble. Might not the monads have early produced an irritation which invited other infection?

In conclusion, we wish to lay stress on a few points:

1. San Diego County undoubtedly contains many cases of protozoal infection more or less active, as well as many convalescent carriers.

2. Some of these cases from Northern latitudes probably become more active by reason of the climatic change, the effect of a marked change of climate and latitude upon the virulence of protozoa having long been known.

3. All patients presenting obscure bowel symptoms, especially if anemic or achylous, should have the stools carefully searched for parasites.

4. The pathogenicity and behavior of the intestinal protozoa vary under different conditions of climate, latitude, exercise, diet and medicinal treatment.

5. The flagellates (monads) are capable of distinctly pathogenic behavior.

6. The most satisfactory treatment we have applied to the monads up to the present is the double mercury treatment above outlined.

### CHRONIC JAUNDICE—FAMILY TYPE.<sup>1</sup>

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UNTIL a few years ago there was little published in regard to this type of chronic jaundice. In 1910 there was shown at the University of Toronto, to the members of the Interurban Clinical Society, a young man suffering from chronic jaundice, with enlarged spleen, which had existed since childhood, and with periods of exacerbation when the jaundice became more intense. There had been an uncle in the family who had suffered from the same condition, but neither one of them had been incapacitated in any way, and complained only of the persistent discoloration. This case shown was diagnosed as family jaundice, but no other analyses were brought to our attention. Since 1913 a number of articles have been written concerning this disease. The French writers are said to have reported on this affection more fully and elaborately than others, but now several American clinicians have reported cases. The best term to express the disease seems to be splenomegaly with or in chronic, congenital, hemolytic jaundice. The disease is exceedingly rare and its pathology is not understood. It is true jaundice and not pigmentation of the skin, such as occurs in Addison's disease or in what is known as Gaucher's disease, which is also a splenomegaly. As one of the terms of its name expresses, it is a hemolytic and not an obstructive jaundice. The disease clinically is characterized by the striking general chronic icterus, the large spleen, moderate anemia, good general health, and the possible history of more than one case in a family. The etiology of this disease is unknown, its pathology unexplained, and its entity recognition manifest by certain signs and symptoms together with blood and urine changes. There are two theories in regard to its manifest symptomatology as well as its cytologic analysis. One is that there is an imperfect formation of the blood, and the other is that the normal cells are unstable or fragile

<sup>1</sup> Read before the Pittsburgh Academy of Medicine.



and hemolysis follows, due possibly to the presence of unsaturated fatty acids in the blood or reduced cholesterin, which is inhibitive normally. The patient reported had a normal cholesterin content in the blood.

Some of the observers have suspected syphilis to be a causative hereditary factor, but the use of salvarsan has produced increased hemolysis and subsequent increase of jaundice. Others, on the basis that it might occur as an hereditary factor following tuberculosis, have used tuberculin with the effect of also increasing the hemolysis and inciting enlargement of the spleen. Some of the writers reporting cases have emphasized the presence of periodic abdominal pain associated with the patients' symptomatology, but in most cases it has proved to be pain due to gall-stones. My own case, which is reported below, presented no abdominal pain whatever, and no suspicion of gall-stones arose at any time. Thayer and Morris, in 1911, reported a case with this symptom present in whom no stones were found upon operation. Other writers report cases which, with abdominal pain, have had stones removed, the operation not giving absolute relief from this symptom; small stones in the liver ducts have then been suspected.

My own case is a man, aged twenty-three years, an American by birth, and employed as a moldmaker in the pottery works of an adjacent State. He was under my observation continuously for a period of ten days at the Mercy Hospital, having been referred to me by Dr. George L. Hays, and the man has reported to me since every few weeks. His sister, aged thirty years, also seen by the writer, presents exactly the same picture clinically, although no blood or urine examination has been made upon her. Their histories are practically the same, the man complaining only of a large leg ulcer besides the jaundice, and the sister complaining of dysmenorrhea in addition to her icterus. They are otherwise well and live and work as the rest of us. The presence of uterine stenosis in the woman and a talipes equinus in the man may be suggestive hints of congenital factors present in both, some such factor producing the hemolytic jaundice. The chief complaint as stated was general icterus and the ulcer of the leg. He has been jaundiced as long as he could remember, certainly since ten years of age. It has been of equal intensity during this time except when the patient had what is said to have been an attack of malaria, when it became more intense. The diagnosis of malaria is doubtful. Ten years ago he was operated upon by the late Dr. R. W. Stewart, at the Mercy Hospital, for the talipes equinus mentioned before, and observations made at that time, with notes, show that the spleen was very large and the patient was jaundiced. This leg ulcer on the left side, the side formerly operated upon, first formed from a small pustule a few years ago, and later broke down, forming an ulcer which has gradually enlarged to a diameter of 2 cm. This ulcer was either due to a varix of the superficial

vein, superinduced by an old phlebitis following typhoid fever at fifteen years of age, or by pressure of the large spleen on the iliac vein.

Family history elicited states that his father is living and well at fifty-two years of age, and his mother died at fifty-two of an unknown cause. Two brothers and two sisters of adult years are alive and well; two children died in infancy; one sister, aged twenty-nine years, reported above, also suffered from this disease. This makes a family of six living children, two of whom are suffering from chronic jaundice. There is no history of carcinoma, cardiac or renal disease, tuberculosis or syphilis in the family. I had no opportunity to test the father for syphilis, such as was done with the patient. The man is a fairly well-nourished individual, showing no signs of serious illness. The skin is warm and soft, and is deeply jaundiced throughout. The pupils are dilated and react to light and accommodation sluggishly. The conjunctivæ are intensely jaundiced.

The oral hygiene was good and the mucous membranes were pale and jaundiced. The physical examination of the thorax was negative. The abdomen presented a unilateral distention on its left half, and the entire skin of the abdomen as well as the rest of the body was deeply jaundiced. The liver was slightly below the costal border, while the spleen was greatly enlarged and explained the distention of the left hemisphere of the abdomen. This organ at this time, April 4, 1916, extended beyond the median line and downward to the brim of the pelvis, with the patient in an upright posture. The spleen also extended upward to the sixth interspace. The splenic notch could be felt 5 cm. below the umbilicus. The urine shows no clinical abnormalities save the presence of urobilin and the absence of bile; it is therefore an acholuric jaundice. The stools are normal in color, indicating the normal presence of bile and not pointing to obstruction to the biliary ducts. The blood shows a moderate grade of secondary anemia, the hemoglobin was 45 per cent., the red-blood cells 3,150,000, and the white-blood cells 11,000. The differential count was proportional. The polymorphonuclear count equalled 77 per cent. The reported cases do not show a leukocytosis, but the leukocytic count is explained by the presence of the leg ulcer. The blood Wassermann was negative. The chronic jaundice occurring in two members of the family, the large spleen, the absence of bile in the urine with urobilin present, and the secondary anemia were the basis of our diagnosis.

The consensus of opinion among clinicians at present seems to be that these cases are very suitable for splenectomy, as the internal secretion of a pathological spleen when plus favors hemolysis, but it would be inexpedient and hazardous to remove a spleen of this size. Heretofore these cases have been treated by iron and arsenic and by the roentgen rays. This patient was treated by roentgen rays once a week, with the hope of reducing the size of the spleen preparatory to a splenectomy. When last seen the spleen, after weeks of roentgen-ray treat-

ment, had been reduced to about two-thirds of its former size, with an increase in the jaundice and in hardness of the consistency. Whether we shall succeed in arriving at a suitable stage is doubtful, but should the spleen be reduced to a manageable size this operation will be urged upon the patient. A prominent clinician recently stated at a public gathering that while he himself would not submit to splenectomy for pernicious anemia, he would have this operation done for chronic congenital family icterus. The after-effects have been striking in some cases, the jaundice entirely disappearing. In the acquired family jaundice the fragility of the cells has been corrected and their normal resistance to hemolysis has been restored; but in the congenital family icterus the cells never regain their normal resistance. The reticulated red cells, of which there is normally 1 per cent. in the blood, looked upon by some observers as indicative of destruction, are probably an indication of regeneration, rising from 5 to 20 per cent. in this disease. The coagulation time and the grade of hemolysis unfortunately were not tried out in this case. Aside from the histological study of the removed spleen the diagnosis could hardly be questioned.

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### THE PRINCIPLE OF BLOOD GROUPING APPLIED TO SKIN GRAFTING.

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GRAFTS may be classified as *autografts*, where the skin is transplanted from the same individual; *isografts*, where the skin is obtained from another person; and *zoögrafts*, where the graft is taken from one of the lower animals. All observers agree that the autograft is the most satisfactory, that a permanent take is least likely or impossible to obtain with zoögrafts, while such uncertain results are obtained with isografts that many surgeons have been led to abandon their use.

With the use of isografts, whether partial or total thicknesses of the skin, a peculiar phenomena has frequently been observed. In the course of the second to the fourth week a certain percentage of these apparently healthy primary takes begin a slight desquamation of the epidermis, then they show signs of resorption by becoming smaller, paler and thinner, and shortly are either reduced to a mere bluish pellicle or have completely disappeared. The grafts apparently fade or melt away little by little. Having had similar experiences, and having seen the uniformly successful results obtained in blood transfusion with matched blood, it occurred to me that the

permanent success of isodermic grafts might be dependent on the same underlying principles.

The present status of blood grouping may be briefly stated as follows: Based on the interaction of serum or plasma and red blood cells, each individual is placed in one of four groups. This classification, as stated by Moss, is as follows:<sup>1</sup>

- AB Group I. Serum agglutinates corpuscles of no person. Corpuscles are agglutinated by serum of Groups II, III and IV.
- A Group II. Serum agglutinates corpuscles of Groups I and III. Corpuscles are agglutinated by serum of Groups III and IV.
- B Group III. Serum agglutinates corpuscles of Groups I and II. Corpuscles are agglutinated by serum of Groups II and IV.
- O Group IV. Serum agglutinates corpuscles of Groups I, II and III. Corpuscles are agglutinated by serum of no person.

Groups I and III are rare groups; Groups II and IV are common. The relative incidence of the four groups, as found by Karsner<sup>2</sup> in 1000 groupings, was: Group I, 3.1 per cent.; Group II, 42.4 per cent.; Group III, 8.3 per cent.; Group IV, 46.2 per cent.

In the transfusion of blood one remembers that the important point is the effect of the patient's plasma on the cells to be introduced. What then can be expected in the transplantation of skin? If one substitutes the term "skin graft" for the "cells" in the above table, like effects may be looked for. It can be readily seen then that if a skin donor is used in the same blood groups as the recipient to be grafted, or if autodermic grafts are used, no resorption of the graft should occur. Going still further with the simile, and adopting the suggestion advanced by Lee<sup>3</sup> and upheld by general usage, that as Group IV blood donors may be used for patients belonging to any of the four groups, because in actual transfusion agglutination does not occur in either direction, so in skin grafting permanent takes may be expected from this "universal donor" class. Such was our experience in every instance. That is, while initial takes were recorded with skin from donors of all four groups, on recipients of all four groups, only autodermic grafts and matched isografts, including Group IV donors, remained permanent takes and continued to grow and expand.

One donor from each of the four blood groups was used for every grafting. Usually all four groups were represented among recipients, and were used as donors of grafts as well. In each

<sup>1</sup> Moss, W. L.: Simplified Method for Determining the Iso-agglutin Group in the Selection of Donors for Blood-transfusion, *Jour. Am. Med. Assn.*, 1917, lxviii, 1905.

<sup>2</sup> Transfusion with Tested Bloods, *Jour. Am. Med. Assn.*, 1918, lxx, 769.

<sup>3</sup> A Simple and Rapid Method for the Selection of Donors, *British Med. Jour.*, 1917, ii, 684.

instance the bloods of both donors and recipients used in the skin-grafting experiments were tested according to the simple and rapid method recommended by Lee, using serums of individuals of Group II and III originally furnished this Base Hospital by Major Lee. In every case Group IV serum was used to check up the results.

For the sake of comparison, Thiersch grafts were used in the first half of the cases and Wolfe grafts in the latter half, with no difference noted either in the primary or the permanent "takes." The long strips of skin thus secured were cut into sections, as recommended by Douglas, Colebrook and Fleming,<sup>4</sup> and either grafted on at once or wrapped in gauze moistened with warm saline until ready for use. An hour was the greatest delay in the latter instance.

As the problem at hand concerned itself entirely with the fate of skin grafts from donors of the four groups, no effort was made to completely cover the exposed areas. Specimen grafts from the same donor or donors of the same blood groups were placed in close proximity to each other, and always one or more of them were near to the margin of the patient's own ingrowing new skin. Careful tracings and notes were kept of the position and progress. We regarded as *primary takes* only those that attached themselves to the surface by epithelization. *Primary failures* were those that did not attach themselves and no epithelial growth remained behind.

In the further progress the primary takes pursued one of two well-defined courses: the first, representing biological compatibility, continued to grow and obviously became a permanent part of the anatomy; the second, representing a biological incompatibility, after a brief period of promise became pale, edematous and gradually faded out, sometimes being cast off as a scale. This might occur any time up to a month or more.

The foregoing is based on observations of 26 different patients, 17 of which are available as evidence. These were successfully grafted with sections of skin from each of the four groups and with autografts. Of these 17 cases, 2 were members of Group I, 8 were in Group II, 2 in Group III, and 5 in Group IV.

GROUP I. Case 1. Amputation stump. Preceding grafting, the stump was ionized daily with 1 per cent. sodium chloride and 1 per cent. zinc sulphate by Captain Baker-Young, R. A. M. C. The grafts of all the groups and the autograft showed initial takes and all continued to increase in size and to be healthy in appearance when the patient was evacuated twenty-three days later. (See Group I, Case 1.)

Case 2. Tangential shell wound in the region of the left knee. On the twenty-third day after being wounded the granulating sur-

<sup>4</sup> On Skin-grafting: A Plea for its More Extensive Application, *Lancet*, London, 1917, xciii, 5.

face was covered with a section graft from each group and one autograft. Seven days later all of the original grafts except that of Group III, which was accidentally removed with the first dressing, were still on. Primary takes of all the remaining groups were present on the eighteenth day. On the twenty-eighth day all grafts had continued to grow as permanent takes and were connecting up with one another and with the patient's own marginal skin growth.

GROUP II. Case 1. Amputation stump. Thiersch skin grafts from donors of each of the four groups and from the recipient himself were applied to the stump surface on January 27, 1918, and again two weeks later. Following neither operation did a Group I, III or autograft take, while strong firm skin was obtained with another Group II and a Group IV in the first and with a different Group IV in the second instance, all of which had continued to grow and increase in size up to the time of evacuation, twelve days later.

Case 2. Amputation stump. Autografts and grafts from donors of each of the four groups were grafted on the stump surface and all took. Between the eighteenth and twenty-third day the Group I and III graft takes grew rapidly smaller and fainter and finally disappeared. Takes from two different Group IV donors and one from the recipient were firmly established and growing when the patient was evacuated twenty-five days later.

Case 3. Amputation stump. One isograft from each of the four groups and one autograft were put on and all had established takes thirteen days later. During the four weeks preceding evacuation the Group I and III grafts diminished to almost pin-head size while the Group II and IV and autograft had more than doubled in size and were firm and healthy. (See Group II, Case 3.)

Case 4. Amputation stump. Surface grafted with several sections of skin from each of the groups and from himself. Takes from all groups were present two weeks later. By the eighteenth day, however, the Group III were faded out. The Group I take gradually decreased in size during the first three weeks, then remained stationary in size for two weeks more, while the recipient's own proliferating epithelium surrounded it and during the sixth week was cast off as a dry scale, leaving takes from two different Group II donors; two different Group IV donors and an autograft growing.

Case 5. Amputation stump. Autografts and grafts from all the groups made primary takes. Group III takes from two different donors became steadily smaller and faded out after three weeks. During the fourth week the Group I take, which had decreased in size, became film-like and disappeared. When evacuated on the thirtieth day only members of Groups II and IV were on. These had steadily increased in size and in one large area had joined up with one another and with the recipient's own surrounding ingrowing skin.

Case 6. Amputation stump of left thigh was grafted with his own and with skins from donors of the four groups. Only autografts took.

Case 7. Amputation stump. Autografts and section of skin from all four groups put on stump a week later. Only autografts became established.

Case 8. Gutter wound of right thigh was grafted with two Group III and one Group II graft five weeks later. Only the Group II graft was a permanent take.

GROUP III. Case 1. Grafts from all groups and autografts were applied on an amputation stump surface. All took. Grafts of Group I and II decreased in size and disappeared during the fourth week. When discharged at the end of the seventh week two Group IV, one Group III and one autograft remained as permanent takes. (See Group III, Case 1.)

Case 2. Amputation stump surface grafted with skin from a donor of each of the four groups and with autografts, but only one autograft was a permanent take. The grafting was repeated a month later, using all groups, but only Groups III, IV and autografts took. When evacuated one month after the second operation two Group III grafts, one Group IV and two autografts remained as permanent takes.

GROUP IV. Case 1. Shell wound of left thigh. Had two severe secondary hemorrhages and was given 750 c.c. of blood of his own group (Group IV) each time; amputation was done after the second. Forty-six days after injury a thick autograft was removed and applied on the stump, along with similar pieces of skin from donors of each of the four blood groups. In ten days takes from all groups were healthy, large and nearly as thick as the original grafts. From the seventeenth day on to the thirtieth, Groups I, II and III began to shrink and grow steadily thinner and paler. When evacuated on the forty-second day, Groups I, II and III had nearly disappeared while the autografts and isogroup grafts were large, thick and healthy, and in the case of the former were being incorporated with the patient's own ingrowing skin.

Case 2. Extensive burns of the inner aspect of the right thigh from shell explosion. Section grafts from the recipient and from donors of each of the four groups were applied. All of these grafts took and continued to grow equally well for three weeks, when in the course of a few days the members of Groups I, II and III became thin and pale and faded away, leaving only several strong Group IV and autografts behind, which continued to be healthy and increase in size until the twenty-eighth day, when the patient was evacuated. (See Group IV, Case 2.)

Case 3. Amputation stump. Grafts from the four groups and from the patient himself. The original grafts of skin were off and found to be replaced by strong healthy takes two weeks later. About

the twentieth day the Group III primary takes began to resolve and were off a few days later. During the fourth to the seventh week the Group I and II grafts appeared to shrink in size, but at the same time they joined up each with the adjacent skin of the same group. By the seventh week the grafts of Group I had grown very small, while two of Group II came off, leaving the third as a minute pale island. In the meantime three of the Group IV grafts and the autograft extending rapidly by peripheral growth joined one another and at the time of evacuation, the beginning of the ninth week, had covered nearly a quarter of the stump surface.

Case 4. Amputation stump. Autografts and grafts from several different donors of each of the four groups were put on the stump surface. Of these one each of Group I, II, III, two isogroup IV and two autografts took. The Group I and II takes disappeared rapidly during the following week, leaving large flourishing Group III and IV grafts. During the last of the seventh week the Group III graft suddenly became pale and disappeared in the course of a few days. When evacuated eight weeks after being grafted only autografts and isografts remained, and these had joined up by peripheral extension and were normal in appearance.

Case 5. Large tangential shell wound of right deltoid. Grafted two weeks after injury. Section autografts and grafts from each of the four groups were used. All were established ten days later. The Group I and II takes had disappeared by the twentieth day and the Group III take during the last of the fourth week, leaving one Group IV graft and two autografts.

*Initial takes* occurred independently of group compatibility; but *permanent takes* were modified by biological compatibility as follows: Group I patients grew skin from donors of each of the four groups and equally well. Group II grew isogroup grafts and grafts from Group IV, while primary skin takes from Group I and III donors in the course of time either shrunk to minute size or entirely disappeared. Group III recorded only skin from the same group and Group IV as permanent takes. Permanent takes from the same group only were obtained in the case of Group IV recipients.

SUMMARY. 1. Autografts grow best.

2. Isografts obtained from donors of the same blood group as the recipient or from Group IV donors became permanent takes and grew almost if not equally as well as autografts.

3. Isografts where the donor and recipient were of different groups did not remain as permanent growths except when Group IV skin was used or when the recipient was a member of Group I.

4. Group I recipients grew permanent skin from donors of all of the four groups and apparently equally well.

5. Group IV skin grew permanently on recipients of all groups, but only Group IV grafts and autografts remained as permanent takes on Group IV recipients.



6. It appears that skin grafting obeys the principle of blood grouping, as in the transfusion of blood.<sup>5</sup>

I desire to render thanks to Colonel Meek, R. A. M. C., Colonel Pilcher, R. A. M. C., Colonel Crile and Colonel Lower, M. C., U. S., for facilities given for this investigation; to Captain Karsner, Captain Eisenbrey and Lieutenant Richardson, M. C., U. S. A., for doing the laboratory work; and to Sergeant Brownlow, who made the illustrations; also to the entire staff of this Base Hospital, whose coöperation is greatly appreciated.

### THE DIFFERENTIAL DIAGNOSIS BETWEEN MITRAL STENOSIS AND AORTIC INSUFFICIENCY.

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THE fact that certain cases of mitral stenosis exhibit a diastolic murmur at the base and certain cases of aortic insufficiency exhibit a presystolic murmur at the apex makes the differential diagnosis between the two conditions a matter of some difficulty and of great interest. In pursuing the study of the cases of mitral stenosis and aortic insufficiency seen in the draft examinations, we outlined a routine which we endeavored to follow in each case. This routine included history, location and character of the apex-beat, including thrills, the outline of the cardiac borders with reference to the mid-sternal line, the location and characteristics of the murmurs, blood-pressure studies with arm by the side, arm above the head (patient standing), pressure (recumbent) in the leg and in the arm, vascular signs, including Corrigan pulse, capillary pulse, Traube's sign and Durossiez's sign.

Two questions we have put to ourselves to answer: (1) What is the criterion or what are the criteria which help one in the differential diagnosis? (2) How frequently does it become necessary to distinguish between mitral stenosis with a Graham-Steell murmur and an aortic insufficiency with a Flint murmur?

History, upon which so much importance is laid in civil life, helps us very little with the draft cases. We have found two types of histories: (1) that of severe rheumatic fever in individuals with perfectly normal hearts who do not wish military service and who know how much emphasis is laid on a history of this nature, and (2) that of perfect health throughout their lives given by individuals with

<sup>5</sup> While completing this report, two suggestions as to the desirability of using matched skin grafts have come to my notice: Davis, J. S.: Some Problems of Plastic Surgery, *Annals of Surgery*, July, 1917, p. 89. Masson, J. C.: Skin Grafting, *Jour. Am. Med. Assn.*, 1918, lxx, 1581.

badly damaged hearts who want to serve. The latter type complain of no symptoms and insist that they have sound hearts, but who finally admit, when told that they are absolutely disqualified, that they have had heart trouble for a long time. Therefore, we are inclined to discount the anamnesis. Stress is often laid on the fact that if there is a rheumatic history the mitral valve is affected, if a syphilitic history, the aortic. How untrue this is those who have had large experience in cardiovascular work will testify. At all events, in our 11 cases of aortic insufficiency which we have carefully studied, rheumatism occurred 4 times in the history, syphilis but once and in 6 cases there was a history of neither. However, in these army cases it is unwise to lay too much emphasis on what the individual states, and reliance should be placed on what the examiner himself finds.

**VISUAL AND PALPATORY FINDINGS.** 1. *Apex-beat.* The apex-beat is displaced to the left beyond the 9 to 10 cm. generally held to be normal, and may be in the fifth or sixth intercostal space. (The circumference of the chest and the weight of the individual have some influence on the location, however). There is a tumultuous movement to the impulse, which is not the quick circumscribed beat of a mitral stenosis but extends widely and imparts itself to the left chest wall, which reflects the forceful systole. On palpation the apex-beat humps itself under the hand and the contraction is felt for some time, while in a stenosis the apex-beat is suddenly felt as a single tap, which recedes quickly and does not linger under the palm. Even if there is a thrill in both instances the apex-beat of a stenosis, as we have found it in the draft, is a forceful circumscribed tap or shock, which quickly strikes the hand, being clearly felt, but which as quickly falls away. On the other hand, the apex-beat of an insufficiency is a heave of great force, of extended area and of considerable duration in its contact with the palm, writhing back to rest for the next upheaval. No distinction can be made between the thrill of a stenosis and that of a Flint, and if there is mitral insufficiency as well as stenosis, the location and character of the apex-beat are of little assistance in the differentiation of the two conditions.

2. *Cardiac Outline.* In all cases of aortic insufficiency that we have examined there has been marked hypertrophy of the left ventricle, while in the pure stenosis (no insufficiency) there has been no hypertrophy, or but slight if any. When mitral insufficiency is present, hypertrophy is generally seen, though not to the extent found in aortic insufficiency. The average width of the left ventricle in the aortic cases has been between 11 and 12 cm. from the midsternal line. Cabot lays emphasis on the cardiac hypertrophy at autopsy, which is a finding to be expected, but he does not distinguish, in this respect, between a stenosis simplex and a stenosis with an insufficiency. He claims that one cannot rule out mitral stenosis with insufficiency because there is good evidence of left ventricular

hypertrophy, which is true so far as his autopsies show. It is not wholly true and scarcely partly true of pure mitral stenosis as it occurs in young males, who, as a matter of fact, show but slight if any hypertrophy. Therefore, I am impressed with the absence of hypertrophy as a valuable sign in differentiating between mitral stenosis and aortic insufficiency.

3. *Vascular Signs.* Special attention has been paid to the question of markedly pulsating vessels, Corrigan pulse, capillary pulse, Traube's sign, Durossiez's sign, blood-pressure in the arm and in the leg, persistence of the fourth phase in auscultatory blood-pressure determinations.

(a) *Pulsating Vessels.* In the cases of aortic insufficiency which we have examined, marked pulsation of the carotid, radial, brachial and axillary arteries has been a striking feature. Head-nodding has been noted in a few cases, but this seems to be less pronounced in the draft cases than in the advanced cases of a civil clinic. In mitral stenosis this marked vascular pulsation is inconspicuous or absent.

(b) *Corrigan Pulse.* A pulse of a Corrigan type is by no means an uncommon feature of diseases other than aortic insufficiency. It has been found in mitral stenosis, but never to the degree that it has been observed in aortic insufficiency. It was present in all our cases (11).

(c) *Capillary Pulse.* This is a difficult sign to elicit. The methods in vogue are: (1) To observe the pulsation under the finger nails following pressure. (2) To rub the forehead and look on the irritated area for alternate blushing and pallor. (3) To evert the lower lip and observe the pulsation through a glass slide pressed on the mucous membrane. The first two methods often fail, the third is the best, but glass slides are not always obtainable, so for this reason I have adopted the following procedure, which is simple and yields good results: With the subject facing the light, the lower lip is grasped between the thumbs and forefingers of each hand, gently pulled down and stretched so that the junction between the mucous membrane and the skin becomes whitened. Holding the lip in this position one can readily see a capillary pulsation if present. It was observed nine times in our 11 cases.

(d) Traube's sign was present eight times. To obtain a systolic tone in the arteries we have found it useful to listen over the brachial artery at the bend of the elbow with the arm extended above the head. In the cases in which the Traube sign was not elicited in the iliacs a tone could sometimes be detected in the brachial by this method. It is really an audible Corrigan pulse if one may so express it.

(e) Durossiez's sign was present but twice and is of little help in the diagnosis.

(f) Blood-pressure in the arm and the leg. The marked difference

between the systolic pressure in the arm and in the leg in aortic insufficiency has been offered as a diagnostic point of great value. Our findings are as follows:

Arm.	Pulse-pressure.	Leg.	Pulse-pressure.
150-42	108	210-0	210
170-30	140	258-0	258
134-62	72	182-70	112
200-70	130	270-115	155
138-36	102	270-0	270
188-28	160	270-0	270
178-86	92	290-0	290
140-90	50	162-115	147
135-65	70	168-82	86
136-56	80	172-56	116

Comparing these with 10 cases of mitral stenosis taken at random from our series we find:

Arm.	Pulse-pressure.	Leg.	Pulse-pressure.
116-68	58	138-80	50
122-84	38	160-100	60
135-80	55	168-84	84
120-80	40	168-90	78
122-62	60	148-75	73
155-85	70	178-110	68
138-70	68	150-88	78
136-80	58	158-92	66
152-95	57	176-98	68
115-75	40	156-88	68

There is in the mitral stenosis cases a difference between systolic pressure in the arm and the leg of 40 to 50 mm. Hg. In the aortic cases the difference may be as much as 130 mm. Hg. and in certain cases leg pressure is double that in the arm. When there is a difference over 60 mm. Hg. the lead is toward aortic insufficiency, although if below 60 there is no certain proof that aortic insufficiency does not exist.

(g) Pulse-pressure. Of equal importance, if not of more value, I believe to be the high pulse-pressure. The average pulse-pressure in health is between 45 and 55 mm. Hg. By examining the above table the high pulse-pressure in the arm and leg in aortic insufficiency is in marked contrast to the pulse-pressure in cases of mitral stenosis.

4. *Auscultatory Signs.* The murmur of an aortic insufficiency may be heard to the left of the sternum as well as in its normal habitat to the right of the sternum, so one is not particularly assisted from the standpoint of location. The Graham-Steell murmur is always heard to the left of the sternum. The character of the murmur is of little assistance, as that of aortic insufficiency may closely resemble that of the Graham-Steell. The latter murmur, however, is a localized murmur and is seldom transmitted beyond its area of production, whereas an aortic murmur is generally transmitted down the sternum.

The apical murmurs of an aortic insufficiency and a mitral stenosis may resemble one another, but there is this difference, that the Flint murmur is associated with a thumping, thudding first sound, whereas the true presystolic murmur of a mitral stenosis is followed by the snappy first sound.

The Flint murmur was present in our series twice in 11 cases (18.1 per cent.), and the Graham-Steell has been found twelve times in 36 cases (33.3 per cent.). A differential diagnosis of considerable interest if not of great importance from the practical side (as in either event the recruit should be rejected) must be made in quite a large number of cases.

**CONCLUSIONS.** The differential diagnosis rests on the findings revealed by inspection, palpation and percussion, with the auscultatory findings, excepting the quality of the first sound at the apex, holding a subordinate place. The most important features in favor of the diagnosis of aortic insufficiency (not arranged in the order of importance) are: (1) Displacement of the apex-beat. (2) Heaving feel of the apex impulse to the palpating hand. (3) Hypertrophy of the left ventricle. (4) Vascular signs, *i. e.*, marked pulsation of vessels, Corrigan pulse, capillary pulse, systolic tone in brachial, with arm above the head. (5) Blood-pressure increase of pulse-pressure, marked discrepancy between the arm and the leg pressures.

In favor of a mitral stenosis are—

1. Loud snappy first sound at the apex unless marked by an insufficiency of the mitral valves.
2. Absence of apical displacement and of cardiac hypertrophy.
3. Systolic tap or shock to the palpating hand.
4. Absence of vascular signs.
5. Absence of any characteristic blood-pressure phenomena.

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## THE CARDIOTHORACIC RATIO: AN INDEX OF CARDIAC ENLARGEMENT.

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THE question of heart size, especially in its relationship to hypertrophy and dilatation, is important to the civilian as well as to the military physician. Its knowledge is necessary in the diagnosis and interpretation of certain systolic murmurs as well as in the prognosis of cardiac, nephritic and vasosclerotic conditions.

For example, a systolic murmur at the apex, with the definite knowledge of cardiac enlargement, will certainly differentiate an

actual valvular insufficiency (endocarditic or myocarditic) from a functional murmur. Without such knowledge an accurate diagnosis is often impossible.

Let us see how important this knowledge of the size of the heart would be in prognosis. To illustrate this we need not go very far. For instance, a case of chronic nephritis with cardiac enlargement is surely of graver significance than without it. The same might be said of cases of hyperthyroidism in which cardiac enlargement would indicate permanent damage to the heart by the thyrogenic poison. Thus one might go on indefinitely with such examples. Suffice it to say, however, that enough instances might be found to warrant investigation into problems that might yield us a method of exact, yet simple determination of the cardiac size.

Cardiac hypertrophy and dilatation are terms frequently used though seldom verified except in conditions of extreme enlargement. Errors in this direction are common enough to justify us in the opinion that many a diagnosis is confused because the method of estimating the heart's size is faulty. This fact was brought out quite strikingly when the writer was engaged in heart work in the Army.

The physician in private practice relies upon percussion for the determination of cardiac size. But to percuss out a heart accurately for diagnostic purposes requires fine technic and is, at best, difficult, especially when slight or moderate enlargement exists. In fact, the London School of Cardiologists denies its possibility altogether even by the most expert. Personally, I cannot accept this extreme viewpoint. To me it seems that much information may be obtained by careful percussion of the heart. I must admit, however, the difficulty occasionally experienced and the great possibility of error.

The location of the position of the apex-beat for the same purpose has recently been reclaimed by Thomas Lewis and his disciples. Our experience on this point has shown us that the reliability of this sign as an index of cardiac enlargement is only moderate. It is of no help in early cases in which the apex-beat is little if at all displaced. This much may be said: (1) that cases of marked enlargement will cause displacement of the apical impulse to the left of the midclavicular line and sometimes downward; (2) that in spite of cardiac enlargement, such as must exist in definite forms of aortic regurgitation, the apex-beat is often within the midclavicular line; (3) that widely diffused apex-beats, as often occur in thin, nervous individuals, frequently seem outside of the midclavicular line even though the heart be unusually small; (4) that occasionally the point of maximum intensity cannot be located because of the diffusion of the apex-beat.

The other methods of investigating the heart's size are the instrumental ones. They consist of polygraphy, electrocardiography and orthodiography.

The polygram is occasionally useful in the determination of right ventricular hypertrophy. In this condition the outstanding feature is the retraction or negative type of apical pulsation. (See Fig. 1.)

But this can usually be visualized on the chest, so can the retraction of the third, fourth and fifth interspaces on the left side and the negative type of epigastric pulsation. By physical examination as much information is elicited as by the polygraphic studies. Thus the usefulness of the latter is minimized.

The electrocardiogram is very reliable. Enlargement of the auricle is evidenced by an increase in the size of the *P* wave. Hypertrophy of the ventricles is indicated by the downward displacement of the *R* wave in one lead and the lessening of its amplitude in another direction. Thus in right ventricular hypertrophy, such as in a case of mitral stenosis, one would get such a tracing. (See Figs. 2, 3, 4, 5, 6, 7.)

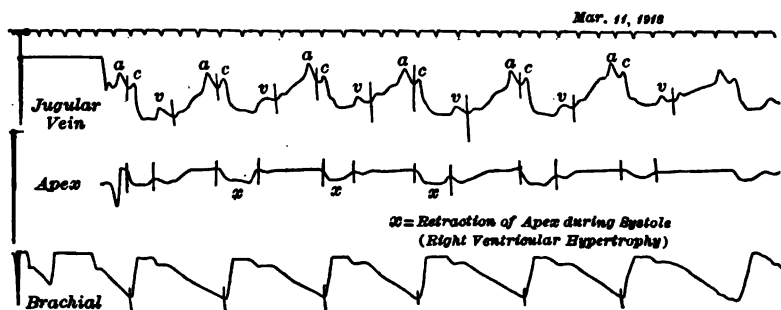


FIG. 1

The disadvantage, however, is that electrocardiography, which requires special training and technic, is not within the reach of the average practising physician. It must be repeated here that we started out to find a simple and easily applied method that should be sufficiently accurate for scientific diagnosis.

Hence we come to the orthodiagram or the roentgen-ray plate taken with the tube at six feet or more from the patient. This distance is chosen because of the divergent or enlarging effect of roentgen rays which occurs when the tube is placed nearer the patient than six feet. At this distance the rays become parallel, thus casting a true image of the heart on the roentgen-ray plate.

This method is simpler and quicker than the original orthodiagraph of Levy-Dorn and Groedel.

The roentgen-ray image of the heart is then perpendicularly bisected and the distance to the right and to the left of the median line is recorded. Thus we say the left border is 8 cm. and the right 3.5 cm. from the midline.

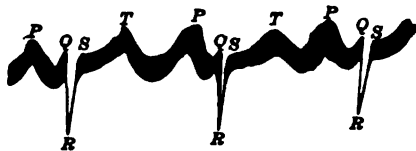


FIG. 2.—R, downward in Lead I.

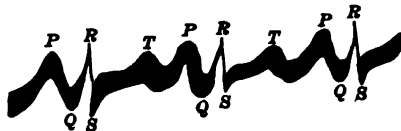


FIG. 3.—R, small in Lead II.

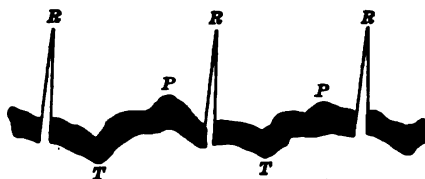


FIG. 4.—R, Upright in Lead III.

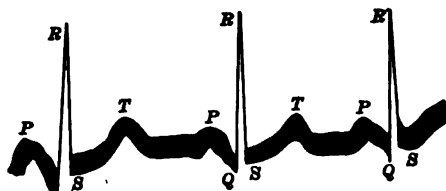


FIG. 5.—Left ventricular hypertrophy. R, upright and large in Lead I.

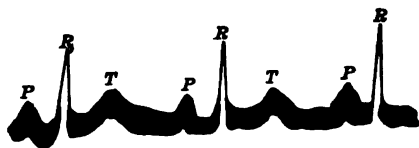


FIG. 6.—R, smaller in Lead II.

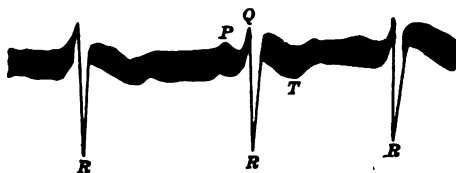


FIG. 7.—R, inverted in Lead III.



This method, though apparently reliable, is objectionable because there are no absolute standards for normal individuals with which to compare the resultant figures. Some text-books, however, give 4.4 cm. to the right and 9.1 cm. to the left as the upper marginal limits. I cannot agree with them, because I have seen absolutely normal hearts in which the left borders were as much as 13 cm. from the midline, while in cases of chronic valvular disease with undoubted hypertrophy corresponding diameters from 7.5 to 9 cm. were not rarities. Although paradoxical on the surface, its truth was many times emphasized on the writer.

This leads us to the question of the comparison of the cardiac diameters before and after the onset of valvular disease. If this were practicable, it would certainly tell us whether or not the heart in question was enlarged. For example, an adult develops rheumatic fever and the roentgenogram shows the left cardiac border to be 8.5 cm. and the right border 4 cm. from the midline. He develops in the course of his illness mitral valvular disease. Two years later the orthodiagram shows the l. b. to be 9.5 cm., and the r. b. 4.5 cm. from the midline. Thus the transverse diameter of the heart has increased 1.5 cm. It is apparent that a hypertrophy has taken place, principally of the left ventricle. Such information in the case of a systolic murmur heard at the apex would help a great deal in the diagnosis and the prognosis of the same.

Perhaps this question is being overemphasized in this article. If so, it is because of the numerous errors seen especially in military practice, where the diagnosis of mitral valvular disease was made altogether too frequently; certainly more so than is warranted by the lessons learned at the autopsy table. Also the diagnostic differentiation between the organic and the functional systolic murmur by the usual methods is inadequate.

In discussing comparative measurements of the cardiac diameters on the roentgen-ray plate before and after the onset of the heart affection I have chosen an adult for an example.

In a child whose heart is naturally growing, comparative measurements would be less valuable, because here an increase in the diameters could not be interpreted as indicative of hypertrophy.

Inasmuch as comparative mensuration such as was described would not be practicable, have we any other means of comparative measurement that could be of help? This calls for an affirmative reply.

It is based on the fact that the heart bears an almost constant relationship to its surrounding framework, the chest. This is seen in the narrow vertical type of heart found in association with the long status asthenicus chest. (See Fig. 8.)

The wide emphysematic chest has a heart of corresponding breadth and one which is more transverse and at a higher level than in the status asthenicus type.

These are the two extremes. Between them are numerous intermediary gradations. The outstanding feature in all of these is the parallelism between the form of the heart and that of the chest, as well as the constancy of the ratio between the transverse cardiac diameter and that of the thorax. (See Fig. 9.)

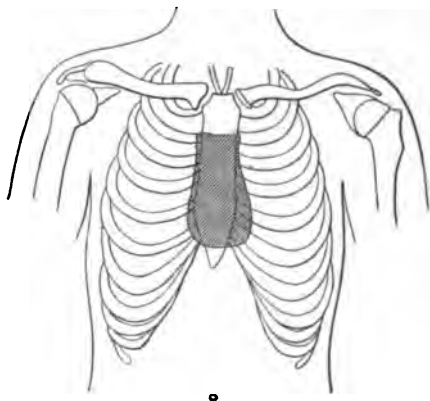


FIG. 8.—Heart, vertical, narrow "drop heart, found in status asthenicus.

It follows, then, that the newborn child, destined to be a person of asthenic proportions, will have a long tube-shaped or "drop" heart, which is the more primitive heart embryologically. The latter

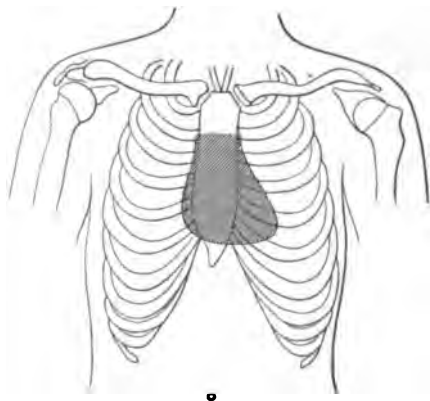


FIG. 9.—Heart, broad type, characteristic of habitus emphysematicus.

is more closely allied to the single tube from which the embryonic heart develops. Likewise the child with an emphysematic predisposition will have a heart that is in proportion to its wide chest.

This relationship is very constant, because of the parallelism in the growth of the heart and that of the chest wall. The only time

there is any divergence at all is during childhood. Then the heart is a little wider proportionately, more round and lies more transversely than in the adult.

This, however, does not limit the scope of application of the relationship of the heart to the thorax for diagnostic purposes. The heart diameters in children have been studied by Sawyer<sup>1</sup> and Voith.<sup>2</sup> With their results as a basis, deviations from normal can be detected in children by comparison with the figures of the above authors.

The former found in his study of 500 young children that the apex was outside of the mammillary line in 63 per cent. of the cases. Voith, as the result of his studies, says that the hearts in children are apt to be rather right sided, the distance to the right of the median line being 50 per cent. of that to the left. In adults, of course, the right diameter is less than 50 per cent. of the left.

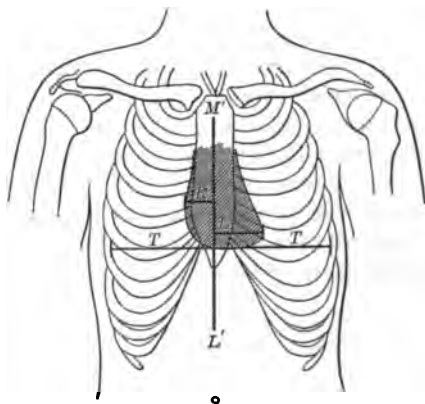


FIG. 10.— $M L'$ , midline;  $R$ , from  $M L'$  to right border (fourth space);  $L$ , from  $M L'$  to left border (fifth space);  $R + L$ ,  $T. H.$  (transverse diameter of heart);  $T. T.$  (transverse diameter of thorax);  $C. T.$  (cardiothoracic ratio) =  $\frac{T. H.}{T. T.}$ .

Hence, in children we expect a high figure for the cardiothoracic ratio and the right side is slightly more prominent than in adults.

Then for practical purposes we may say that ratio between the size of the heart and chest is quite constant except when pathological processes set in. Then the relationship is disturbed, *e. g.*, the onset of valvular diseases will cause an enlargement of the heart without any accompanying change in the size of the chest. Thus it is seen that cardiac enlargement will show itself as an increase in the cardiothoracic ratio, if the latter is obtained by dividing the transverse diameter (right and left diameters) of the heart by that of the thorax taken at a given level.

Therefore, we studied a sufficiently large number of cases in order

to establish the normal ratio. We also had to determine at what level we would take the chest measurement.

We finally decided on taking the thoracic measurement at its greatest diameter, which is usually at the level of the apex or one space lower and measuring to the inner borders of the ribs.

The cardiac measurements were also taken at their widest points. Usually it was the fifth space on the left side, the fourth space on the right. We used the metric scale. (See Fig. 10.)

A word ought to be said concerning the taking of the plate. The patient should be in the upright position and breathing should be shallow. The operator should wait until the initial excitement of the patient passes off. If this precaution is not heeded the cardiac excursions between systole and diastole will be great enough to cause an appreciable difference in the measurement of the heart therefore in the cardiothoracic ratio and in the interpretation of the same.

The patient should stop breathing in midinspiration, for the exposure. If the plate is taken at the height of inspiration the heart will be lengthened and narrowed; if at the height of expiration it will be widened and made more round. It will be seen that between these two extremes quite a margin exists.

The thoracic diameter will also vary with the phase of respiration.

However, if the above precautions will be observed the margin of error or of variability will be reduced to a minimum.

We found as the result of these calculations that the normal heart is usually less than half the greatest diameter of the thorax:

$$\frac{\text{Heart (transverse diameter)}}{\text{Thorax (transverse diameter)}} \text{ 39 to 50 per cent.}$$

The average was about 45 per cent.

Because of the possible variations previously described, a margin of safety of 2 per cent. above the upper limit was allowed.

We may summarize as follows: Anything over 50 per cent. was regarded as suspicious. If other evidence pointed against the existence of hypertrophy, values up to 52 per cent. were regarded as normal. However, 53 per cent. and over were considered definitely pathological.

In many of the long narrow-chested individuals with small, "drop" hearts the occurrence of valvular disease and coincident cardiac enlargement will often yield neither an evident increase in the actual nor the relative cardiac size above the standard diameters of normal hearts.

In fact, figures as low as 46 to 47 per cent. (cardi thoracic ratio) are quite common in spite of cardiac hypertrophy. This means that a heart may be absolutely small though hypertrophied. Although apparently paradoxical this fact rests on sufficient proof.

Hence in cardiac hypertrophy the relative size or the cardio-

thoracic ratio may or may not be increased. If it is, it indicates cardiac enlargement. If the ratio is not increased, cardiac hypertrophy cannot be ruled out. In such a case the diagnosis will have to rest on the study of the intrinsic diameters of the heart and the character of the murmur and the history.

It is evident, therefore, that the size of a hypertrophied heart will depend to a large extent on the type of heart and its size before the onset of the cardiac affection. Thus a small heart (Tropfen Herz) may, in spite of a severe aortic regurgitation—which is so apt to produce cardiac enlargement—still remain smaller than the standard diameter for the average normal. The cardiothoracic ratio is very apt to be altered, however.

Incidentally I should like to call attention to the fact that the cardiothoracic ratio is of value in the recognition of a tubercular predisposition. This is based on the view of Brehmer,<sup>3</sup> who said that a small heart with too large lungs is an important element in the predisposition to phthisis.

Hence, when the cardiothoracic ratio is definitely under 45 per cent. it points in favor of tuberculosis in the presence of suspicious lung signs. The lower the percentage the greater the presumption.

**SUMMARY.** 1. The cardiothoracic ratio is based on the anatomical relationship that exists between the heart and its containing frame, the chest.

2. The method of obtaining this information is within the reach of the majority of practising physicians. In other words, wherever a roentgen-ray laboratory exists the facilities are sufficient for this work.

3. The method has been tried out on a sufficiently larger number of cases (some 500 or more) to warrant its practicability and usefulness in the estimation of cardiac size, particularly in cases of moderate or early enlargement.

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**CLINICAL STUDIES IN CUTANEOUS ASPECTS OF TUBERCULOSIS.****III. THE THERAPEUTIC MANAGEMENT OF THE TUBERCULIDS, WITH SPECIAL REFERENCE TO THE EFFICIENCY OF ARSPHENAMINE.**

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IN studies Nos. I and II, I have reviewed the types of purpura, erythema multiforme and erythema nodosum which have a clinical association with systemic tuberculosis, and the diagnostic and clinical aspects of the papulonecrotic tuberculids and erythema induratum. Both of these studies emphasized the interest to the general diagnostician and the internist of this group of cutaneous lesions, which, while not themselves tuberculous in histopathologic architecture, are practically invariably associated with visceral tuberculosis, probably as an expression of bacillary infarction by hematogenously distributed tubercle bacilli plus cutaneous allergy.

In this study, the final one of the series, it is proposed to give an account of the method developed for the treatment of the papulonecrotic and erythema induratum types of tuberculids on the service of the Section on Dermatology. The report is based on 20 patients treated in a series of 30 under observation. It is intended to give primary emphasis to the effect of arsphenamine on the lesions and on the constitutional condition of these patients. None the less, a fundamental conservatism must underlie such a report. The longest period of observation reported is twenty-four months, and in all the cases adjuncts to the arsphenamine treatment, in the form of constitutional measures, roentgen ray to visible tuberculous foci, etc., have been employed. The ease with which *post hoc* thinking may be indulged in under such circumstances is fully appreciated, and for that reason what follows is to be interpreted as a preliminary report, albeit some attempt at critical analysis of the various factors in the treatment régime is made.

**SUMMARY OF THE CLINICAL ASPECTS OF THE SERIES.**

For a fuller study of the clinical aspects of the group of tuberculids herein discussed, reference should be had to the previous studies. By way of summary it may be said that of the 20 treated patients, 6 presented the tuberculid known as folliclis, 1 had acnitis, which is the papulonecrotic tuberculid of the face, 8 had papulonecrotic tuberculids involving the trunk, 8 presented lesions of erythema induratum on the legs, 3 had tuberculous erythema nodosum, in association with other tuberculids, and the condition was quiescent in 3.

*Visceral Lesions.* Ten of the 20 patients (50 per cent.) had demonstrable tuberculous lymphadenitis in situations that were at least in part accessible to local therapeutic measures such as roentgen rays and surgery. Of the remaining 10 patients, 8 were "occult" or obscure cases, exhibiting no recognizable physical signs, with the exception of one who showed evidence of tuberculous involvement of the right apex with a negative roentgenogram. Three patients had positive Wassermanns without adequate objective evidence of syphilis, a condition discussed in Study II of the series. Four of the 10 patients having tuberculous lymphadenitis showed suggestive or diagnostic roentgenographic signs of pulmonary tuberculosis.

All the patients belonged to a type of tuberculous subjects having a high native resistance to the infection. None of them was acutely febrile or rapidly progressive. Several were fat and florid and to all outward appearances in robust health, conforming thus to a type which is familiar in association with visceral tuberculosis. The remainder were of smaller stature and slighter build, exhibiting a moderate pallor with asthenia, and, with surprising frequency, arthralgias and myalgias of the type usually associated with pyogenic focal infection. Several of the patients had mild grades of anemia, with afternoon temperatures fluctuating between 99° and 99.6°. Cough, hemoptysis and night-sweats were notably absent in the group as a whole. Loss of weight had occurred in a number of instances. In the overwhelming majority the cutaneous tuberculid was chronic, showing little disposition to remission and almost none to total disappearance. The group was therefore a good one in which to employ new therapeutic methods, since the presumption was strongly against spontaneous remissions in the guise of therapeutic effects. A number of the patients have shown the characteristic tendency to spring exacerbation, and several of these have now been carried through one and even two such periods without remission.

#### SPECIAL TREATMENT OF THE TUBERCULOUS FOCUS IN ITS RELATION TO A TUBERCULID.

The surgical work of the clinic has provided the opportunity to study, in connection with our work, the value of the surgical treatment of a tuberculous focus as a means of influencing a tuberculid. In estimating the effect of surgical extirpations of glands, however, it must be recalled that, as conventionally performed, such measures fall short of complete extirpation of the focus, and that results which such incomplete procedures fail to achieve can hardly be laid at the door of adequate surgery. On the other hand, the popularity of surgical treatment for axillary and cervical tuberculous adenitis justifies an estimate of the gross operative outlook when compared

with a proposed medical procedure for accomplishing a similar purpose.

A survey of 100 cases of tuberculous glands undertaken as a preliminary indicated that 37 per cent. of the patients had sustained one operation, 26 per cent., had been operated on twice, and 37 per cent. had been operated on more than twice. The highest number of operations sustained by any one patient was eight. The frequency of repetition noted must, of course, be ascribed, in part, to the impossibility or inadvisability in certain cases of attempting to extirpate a focus by a single procedure, and also, of course, to the inadequacy of the technic employed in some cases. None the less, the figures are suggestive in the light of our findings in patients with tuberculids. Nine of a total of 30 patients had received operative treatment in the form of excisions of glands for tuberculous adenitis. Three had had one operation with relapse; 2 had had two operations with indeterminate results; 3 had had two operations with relapse and 1 had had three operations and relapsed. Surgery had not, therefore, as applied in these cases, been conspicuously successful in eliminating the focus. In its relation to the tuberculid the following facts appeared:

The cutaneous outbreak had followed the operation in 4 cases, 3 after the first operation and 1 after the second. Operation had no effect whatever in 5 cases. In 1 of these one operation had failed, in the other three operations had been done without effect on the tuberculid. In 1 case constitutional benefit was reported, but the tuberculid persisted.

While due allowance must be made for the smallness of this group of cases, and for the unfairness of expecting one operation to accomplish what three may be necessary for, this much may be said to appear tentatively from our examination: Surgical treatment of a tuberculous focus as ordinarily carried out neither guarantees a patient against a subsequent tuberculid nor offers him any worthwhile therapeutic prospect if one is already present.

It should be recalled, in considering this point, that the best available pathologic and experimental evidence points to the belief that a tuberculid means hematogenously distributed tubercle bacilli from an active focus. Its occurrence after operation is, therefore, evidence for clinician and surgeon alike, that operative effort to extirpate the focus has failed. The repeated failure of operation to cure the condition simply registers repeated failure to get at the active process. A number of patients with tuberculids do not exhibit gross foci susceptible of surgical treatment. Forty-four per cent. of our patients showed no focus susceptible of surgical treatment. In such instances retroperitoneal and tracheobronchial tuberculosis and signs suggestive of localized tuberculosis in the abdominal cavity offer a plausible explanation, occasionally demonstrable at necropsy or by roentgenographic signs. It seems reasonable to believe that even in



cases in which there is a grossly obvious focus, such obscure and unreachable accessory foci may also exist. The failure of operation, when reasonably complete, to influence the course of a tuberculid should, therefore, it would seem, be interpreted as a signal to desist and to adopt in the place of further surgical intervention, measures to combat the focus constitutionally, by increasing the patient's resistance and affecting the walling off of the focus by physiologic means. Only a long series of cases can demonstrate, of course, that the medical procedure should have been invoked in the first place and the surgical procedure subordinated to it.

#### MISCELLANEOUS OBSERVATIONS ON TUBERCULIN TREATMENT, ETC.

The patients treated in this series offered opportunity for incidental observation of the effect or lack of effect of a miscellaneous variety of treatment. Of 5 patients with tuberculids, treated with tuberculin, dosage and method of employment unknown, 2 reported themselves as having been made much worse, following violent reactions. One had observed no effect, in another the glands had subsided (cervical lymphadenitis) without affecting the tuberculid, the fifth reported herself improved. I myself have observed the tendency to marked and unfavorable reaction to tuberculin sometimes exhibited by this type of case, with rapid extension of the process and believe that it may be aligned with the hypersensitiveness exhibited by cases of acute disseminating lupus erythematosus, in which reports of fatal outcomes are on record following the administration of small doses of tuberculin (Ravogli). MacKee has recently reported indifferent results in the treatment of a number of cases of the papulonecrotic tuberculid with tuberculin.

Three patients had received vaccines, 2 autogenous and 1 stock, presumably on a diagnosis of acne vulgaris or a pyogenic process. A patient with acnitis was made much worse, 2 others were improved, 1 of them a case of long standing. In an allergic complex such as that which underlies the development of tuberculids, it is difficult to determine the *rationale* of such a procedure, though it is conceivable that the improvement may be due to an action on the secondary focus of pyogenic infection present in more than 50 per cent. of these patients, as discussed in Study II. In both the patients who improved, such foci were present; the one had very septic tonsils and the other alveolar abscesses. This aspect of the therapeusis of tuberculids as well as their pathogenesis deserves further study. The effect of a vaccine, like the probable effect of arsphenamine, may be that of a non-specific stimulation of immunity and of defensive processes rather than a specific action upon the causal agent. One patient had received roentgen therapy to the lesions themselves. She reported that the ordinary dosages and methods were without

effect, but that one "deep" treatment had been beneficial. The *rationale* of this procedure is also doubtful, in view of the pathology of the tuberculid. It is possible that the constitutional effect of intense roentgen treatment accounts for the observed improvement.

Arsenic in other forms than as arsphenamine had been administered to three patients. One had taken enough Fowler's solution to produce palmar keratoses and hyperpigmentation, with little effect on the tuberculid. Another had received no benefit from the same preparation. One patient had received sodium cacodylate for anemia, with fair effect on the tuberculid. Her cutaneous lesions were subsequently cleared up by arsphenamine.

Mercury was intensively administered to 5 patients on the finding of a positive Wassermann. Three of them showed a normal tolerance of the drug by inunction or injection. The other 2 were less favorably affected. One of them was improved by iodides. Four of them noted improvement under arsphenamine. One patient had received iron for the anemia which marked the onset of active glandular tuberculosis, with marked benefit.

Local measures used in the cases observed were of little avail. A surprising amount of meddlesome surgery had been done on some of the lesions, notably when occurring on the leg, even to the point of repeated total excisions of lesions and deep incisions for supposed osteomyelitis, which had so damaged the blood supply of the tissues that satisfactory results could not subsequently be obtained.

*Arsphenamine and Arsenical Synthetics in the Treatment of Tuberculids.* The employment of arsenic in a variety of forms in the therapy of cutaneous tuberculosis has, of course, been familiar practice for a number of years. On the other hand, little of conspicuous benefit has been reported from it except perhaps in the sarcoids, a group of supposed tuberculids still of unsettled pathogenesis. With the advent of a new and highly potent arsenical in the form of salvarsan, an immediate attempt was made to apply it to the therapy of cutaneous tuberculosis. Herxheimer and Altmann, for example, early reported favorable results from its employment and asserted that they observed local reactions from its use similar to those obtained by tuberculin. While this latter observation has not been generally confirmed, other favorable therapeutic reports appeared. Just before the war Ravaut, followed by Tzanck and Pelbois, published accounts of marked benefit to a number of types of lesions of tuberculous origin from courses of salvarsan averaging three to six injections in number. The latter authors also urged the importance of an appropriate hygiene in the management of these cases. Sequeira noted the improvement of lupus vulgaris under atoxyl and salvarsan after mercury and the iodides, previously administered, had failed. The effect of arsphenamine on tuberculous subjects had been experimentally studied by Nicolas, Courmont and Gaté in 1912 and by Courmont and Durand in 1913.

These authors found that in experimental animals a marked increase in agglutinins for tubercle bacilli occurred in the blood on the administration of arsphenamine. Nicolas, Courmont and Charlet found a similar phenomenon to occur in the blood of tuberculous patients, and established at the same time that the increase occurs in those in whom the agglutinins are already high or on the increase rather than in those in whom they are low. In a therapeutic series of pulmonary cases in which novarsenobenzol Billon was given in small doses per rectum at frequent intervals, these authors felt their impression based on experiments, to be confirmed. They concluded that the drug should not be used in progressive or grave cases, which are aggravated by it, but in discrete limited involvements having a tendency to favorable course. The action was compared to that of sodium arsenite and arsphenamine rated as a reinforcement in selected cases. Potter, in summarizing his experience with 21 cases of combined tuberculosis and syphilis, reports favorably on the effect of arsphenamine, but cautious against its use in active, acute and miliary cases. He also noted the occurrence of tuberculin-like focal reactions.

My own experience with arsphenamine as represented by the types of tuberculous involvement included in the present series of cases is in accord with that of the authors mentioned. The effect of the drug does not suggest that of a specific bactericidal agent, but rather that of a fortifier of individual resistance and a means of stimulating the defensive mechanism of the body against the tubercle bacillus. Clinical study does not, of course, establish whether this is accomplished by the increased formation of specific agglutinins as suggested by the work of Nicolas and his collaborators, or by a less specific modification of the allergic and metabolic balance of the patient. My own observations in the use of arsphenamine in double infections with tuberculosis and syphilis accord with that of Potter in opposing the use of the drug in acute or unfavorably progressing cases or in those showing evidence of low resistance. One of the two conspicuous failures in our tuberculid therapeutic series was likewise a case of low resistance, running a rapidly progressive course. The patient died eight months after she was first seen. The ideal type for the use of arsphenamine, so far as our observations thus far suggest, is the patient who, while perhaps not on the up grade, is at least holding his own, who has seasonal periods when his resistance for the time being suppresses or controls all manifestations of the infection, and who rallies from the exacerbations produced by intercurrent ailments without a permanent break in his recuperative powers. The effect of arsphenamine in hastening the healing of ulcerative tuberculids, while not so striking as that in syphilomas, is none the less marked enough to suggest a degree of special action by this drug on granulomatous tissue, comparable to that exerted by potassium iodid, for example. This type of effect

may be similar to the effect of arsphenamine on blastomycosis, and, in my own experience, to the effect on occasional cases of sporotrichosis.

#### THE ARSPHENAMINE COMBINED TREATMENT OF TUBERCULIDS.

The use of this somewhat bizarre phrase is intended to imply that the régime actually employed at the present time on the service of the Section on Dermatology in the Mayo Clinic is a combination of several therapeutic methods, including: (1) The intravenous administration of arsphenamine or neoarsphenamine, (2) the roentgen ray to detectable and accessible foci of glandular tuberculosis, (3) an antituberculous outdoor régime, (4) a forced diet, (5) the removal of secondary foci of pyogenic infection in tonsils, teeth or elsewhere, and (6) the correction of vascular stasis and vasomotor abnormalities involving the extremities. Two items usually emphasized in texts we have found to be of secondary importance, that is, rest and local treatment of the lesions. It has been our experience that the former while of value need not be carried to the point of rest in bed with elevation of the affected leg.

*The Arsphenamine Treatment of Tuberculids.* Our preference in the selection of the preparation of arsphenamine is for arsenobenzol Polyclinic (Schamberg), although we have occasionally employed novarsenobenzol (Billon). The rather marked tendency to reaction exhibited by these patients has led us to prefer the former because of its exceedingly low toxicity and because of the same tendency to a lower intrinsic toxicity of the dihydrochlorate as compared with the monomethylene sulphonylate of sodium salt which is observed in syphilis. The drug is given in courses, with a view to taking advantage of its cumulative effect. The average course is six injections, though later courses may be shortened. The dosage must draw a compromise between a maximum introduction of arsenic and the avoidance of toxic and debilitating effects from overdosage. The initial dose should not exceed 3 decigrams, the average dose 4 to 5 decigrams of arsphenamine or its neoarsphenamine equivalent. The injections should be given at weekly intervals. For the first 2 or 3 patients of our series, and for 1 seen subsequently but treated elsewhere, the dosage was small and the treatment desultory and irregular, to which we ascribe much of the relatively unsatisfactory results. The method should not be adjudged inefficient or inapplicable to a particular case until it has had systematic and persevering application.

At this stage in our employment of arsphenamine I feel it important to emphasize the repetition of the course as a seasonal reinforcement of the patient in the months of the year in which the tendency to relapse is usually greatest, that is, in March and November. In our series of 17 active cases, 4 patients received short courses of

four or five injections each, 6 have received thus far one course of six injections each, 3 received initial courses of eight injections. Three received two courses, totalling from eight to ten injections. Two received three courses, totalling ten and sixteen injections, respectively. One patient has received five courses, totalling twenty-four injections. The improvement exhibited by a given case is only incidentally a function of the number of courses. By estimating the total dosage in terms of grams of arsphenamine there is apparent, however, a relation between the total dose and the degree of improvement. Of 5 cases in which the improvement was rated as 4 on a scale of 0, 1, 2, 3, 4, the average dose was 3.8 gm. This omits from consideration 1 of our most remarkable cases, which was transformed by a total dosage of 10.8 gm., too high to be fairly compared with the other 5. Of the remaining cases, in which the patients showed improvements ranging from 0 to 3 and averaging 2 plus on the same scale, the average total dosage was 2.6 gm., or 1.2 gm. less than the dosage of the 4 class.

Improvement under treatment must be considered under three heads: (1) improvement in the cutaneous lesions of the tuberculid, (2) improvement in the constitutional condition of the patient, and (3) improvement in the tuberculous focus if observation of it is possible.

The improvement effected in the tuberculid by the administration of arsphenamine is often the first change apparent under treatment. Usually with the first and second injections, but sometimes not until the fourth, there are marked drying and reduction in the size of any active lesions present and a diminution in tenderness. The course of any new lesions which may appear is markedly shortened and the number of recurrences greatly decreased. In a case which is progressing favorably, new lesions have ceased to form by the end of the first course, although even in cases which ultimately remain clear there may be slight relapses. In several of the cases in our series which were at first rated as failures the patients have recently reported that they consider themselves much improved, owing to the fact that although lesions still appear they have practically ceased to be troublesome.

The treatment results in our series may be summarized from the standpoint of cutaneous lesions as follows: Of 17 patients presenting active lesions, 9 (53 per cent.) have been completely cleared of active lesions, 5 in the first course, 3 in the second and 1 later. Four patients have been improved though not protected from relapse; treatment of these is incomplete. Four cases of the series (24 per cent.) were rated as failures before the sending out of a questionnaire while the present study was in preparation. As a result of this questionnaire it appears that one of the "failures" rates herself as 50 per cent. better than before treatment. She still has nodular recurrences but no ulcers. Her total dosage was 4.1 gm. in ten

injections. The second "failure" reports herself as "a great deal better," and as having gained 40 pounds in weight, although she is again down to medium weight. This was one of our early patients who received unsystematic treatment with rest in bed. The outlook for complete symptomatic recovery was greatly reduced by the amount of surgical trauma inflicted on the legs, which were the sites of most of the lesions. Numerous incisions, excisions and attempts at plastic treatment of the ulcers had practically ringed the affected area about with scar-tissue, creating an artificial stasis. The two *bona fide* failures were a woman with an erythema induratum of the calf of one leg and a tuberculosis verrucosa cutis of the other, with a progressive anemia and asthenia. While no active focus could be identified, she was reported dead in response to a questionnaire. The second failure was in a rather obese woman, a low resistance type, with innumerable scars of suppurating cervical glands and a history suggestive of tuberculous peritonitis with a focus in the adnexa. She had an inadequate early course with overattention to local measures, and relapsed the following spring, with more suppurating glands. If in 2 of the 4 cases described the patients may be rated on their own estimate as improved, the percentage of total failure to improve the cutaneous condition will be reduced to about 12 per cent.

Precisely how much of the constitutional improvement manifested in these patients is to be attributed to the arsphenamine which they receive it is difficult to say. Undoubtedly the storage of arsenic in the liver and spleen which occurs during a course of injections provides the basis for a prolonged tonic effect. On the other hand, a number of our patients showed definite improvement in their general symptoms while receiving the first course of injections, and this in face of the fact that they were not encouraged to adopt any special hygienic measure until the interim between courses, and again in spite of the fact that some of them resumed hard work which they had been physically unequal to prior to beginning their course of injections.

Gain in weight and an improvement in or complete disappearance of "rheumatic" symptoms if present were the two most immediate and conspicuous effects on the general health of the patients. The weight gains during the course of treatment varied from 1.5 to 13.5 pounds. The tendency to gain weight continues to manifest itself after the completion of the course, and in fact many of the most striking increases occurred in the month following the arsphenamine treatment, a phenomenon we have repeatedly observed in the treatment of syphilis. While the weight changes are undoubtedly to some extent influenced by forced diet and hygiene, the changes occurring under arsphenamine alone are sufficiently marked to make it probable that the drug was largely instrumental in the improvement.

Of 14 patients on whom definite data are available, not one has failed to register some gain in weight. Seven (50 per cent.) have



FIG. 1.—Acnitis, the papulo-necrotic tuberculid of the face. Scar of operation for tuberculous adenitis visible on the neck. The eruption followed the operation. Photograph taken before arsphenamine treatment was begun.



FIG. 2.—After five injections of arsphenamine—only scars and pigment macules remain.

made gains varying from 7.5 to 40 pounds in periods varying from two to twenty-four months. Four patients gained more than 20 pounds. While the peak of the weight curve is not always maintained, 4 have held gains of 15 pounds or more for from one to two years.

Loss of weight may occur, especially in the obese. Three patients lost from 7 to 10 pounds during their course of arsphenamine injections. This was accompanied by an increased sense of well-being rather than the reverse.



FIG. 3.—Four months later after three more injections of arsphenamine. Complexion clear and blooming.

The effect of arsphenamine on the arthralgias and vague aching pains which many of these patients present is often very striking. A patient who had been operated on for a tenosynovitis without improvement, and who had multiple swollen and painful joints (both ankles and the right knee), was completely relieved of her symptoms by the fourth injection of her first course and has suffered no recurrence. Another, at one time bed-ridden for weeks with "rheumatism," has had no such symptoms since her first course, and only notices a slight aching when extremely fatigued. A barber who registered the maximum weight gain under treatment remarked enthusiastically that he had gone back to earning a living after having been unable to be on his feet for more than an hour a day for two years on account of pain and swelling of the ankles.

While our observations are still too few in number to permit of



generalizations, we have not been impressed with any marked influence of the arsphenamine on the tuberculous adenitis insofar

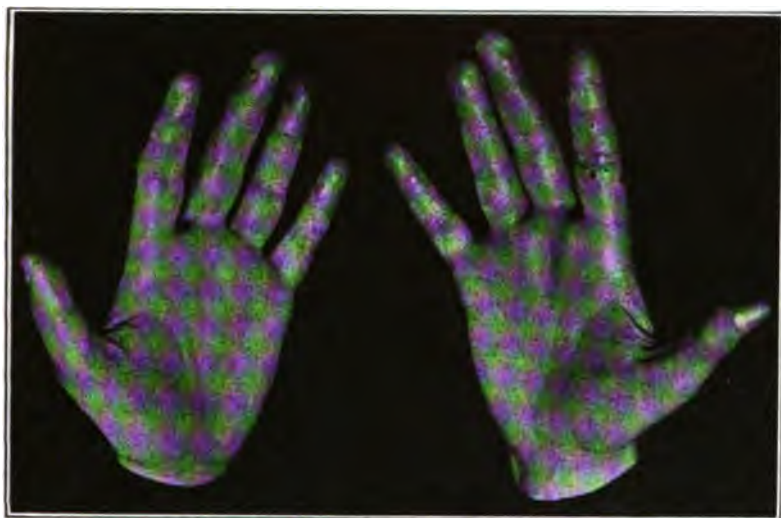


FIG. 4.—Lesions of follicles before the administration of arsphenamine.



FIG. 5.—Same case as Fig. 4. Lesions healed following six intravenous injections of arsphenamine. No other treatment used.

as it can be judged by a reduction in the size of the glands. In 2 cases actual increase in the size of the glands seemed to occur during the early part of the course, and a rapid reduction subsequently followed

the first one or two Coolidge tube exposures. In other cases the glands were very little influenced. Several patients in response to a questionnaire, report reductions in the size of the palpable glands, but such reductions occur so often as a result of improved hygiene and a period of freedom from secondary infections that no conclusions can be drawn.

About 50 per cent. of patients with tuberculids seem to exhibit a distinct idiosyncrasy for arsphenamine, a figure very much in excess of the average reactivity displayed by syphilitics for a similar dosage and interval scale. Of 9 patients, 4 had single or repeated nitritoid crises, 4 had pronounced gastro-intestinal reactions and 1 developed a toxic erythema, a very rare accident on our service. As in the treatment of syphilis, a definite overtreatment syndrome with marked idiosyncrasy, loss of weight, pallor and nervousness is an indication for abandoning arsphenamine.

*Roentgen Therapy.* Our experience with the roentgen ray in the treatment of tuberculids has been largely confined to its use in treating a glandular focus. The earlier technic employed was less efficient than the later, and for that reason no final conclusions are possible. The treatment recently given under the direction of Dr. Jones in the Department of Roentgenology of the Mayo Clinic has consisted of a four and one-half minute exposure with the Coolidge tube on a 4-inch square surface over various parts of the mass, using a current of 5 ma. with a 7- to 9-inch spark gap and a focal skin distance of 9 inches. The filter employed has consisted of 3 mm. of aluminum, 1 cm. of wood and 5 mm. of sole leather. With this technic we have seen a definite effect on glands which we did not believe could be attributed to any other factor in the treatment.

On the other hand, the effect of roentgen treatment of the glands on the tuberculid seems to us more open to question, especially when compared with that of arsphenamine. One patient who improved slightly under x-ray alone registered the most surprising gains under arsphenamine at a considerably later period when the ray had been discontinued and its effects must have worn off. A second patient received x-ray to the glands at intervals without effect on the tuberculid or the glands, but the tuberculid improved subsequently under arsphenamine. In a third patient the lesions were cleared up by arsphenamine and no x-ray was employed until later. Three of six patients presenting a glandular focus made remarkable gains without any x-ray, and in several occult cases in which the patient presented no indication for its use, remarkable improvements were likewise made. While roentgen-ray treatment of the focus of tuberculous infection in a glandular case has its function, it cannot be regarded either as a substitute for arsphenamine in the control of the tuberculid or as comparing with it for promptness and of efficiency in the cases under our observation.

*Outdoor Régimé, Forced Diet and Rest.* Since it is axiomatic that the treatment of a tuberculid is that of the underlying tuberculosis, emphasis has been placed with the patient on these means of cultivating an increased resistance. That their part is to increase the permanence rather than the striking quality of a therapeutic result is the impression derived from observation of those of our series who have adopted our recommendations. A number of patients have made and held marked improvements without giving this aspect of their treatment the attention it deserves. On the other hand, the four or five patients who have been longest under observation and give the greatest promise of permanence have at least slept outdoors, even though following indoor occupations, and have conformed to the general principles of antituberculosis hygiene. Rest, particularly in bed, has not been urged on our patients at any stage, and we have noted distinctly inferior results in our earlier cases when the patients were confined in order to secure the effect of rest on the lesions. Several patients have had notable results while pursuing strenuous occupations, such as housework sixteen hours a day, barbering and heavy teaming.

*Treatment of the Secondary Focus of Pyogenic Infection.* As shown in Study II, a high percentage of patients exhibiting cutaneous tuberculids have a secondary focus of pyogenic infection in the form of septic tonsils, alveolar abscesses and possibly, in some cases, foci, such as infected gall-bladders, etc. When such a focus could be identified we have found it advisable to remove it, although its precise role in the production of the tuberculid is undetermined. Such a removal is not sufficient in itself to cause the disappearance of a tuberculid without appropriate general measures and special treatment directed at the tuberculous focus if it can be identified. We observed in one case, however, that a single obstinate and persistent lesion on the leg which had refused to yield to the régime which had cleared up all the others, healed after the removal of markedly septic tonsils. On the other hand, in several of our patients the tuberculid appeared at varying intervals following tonsillectomy.

*Correction of Vascular Stasis.* The value of the elastic bandage in hastening the involution of papulonecrotic lesions on the legs even in the absence of gross vascular abnormalities, such as varicose veins, was early apparent, and did much to keep our patients out of doors and active. In cases exhibiting vasomotor anomalies, as in the thinner and more neurotic types of patients, two pairs of stockings, silk and wool, or specially warm clothing and gloves, were of value in improving the peripheral circulation and diminishing the severity of recurrences.

*Miscellaneous General Observations.* Taken as a group, the least favorable results are to be expected from the obese, florid types of patients. The majority of them have erythema induratum, and the marked stasis element in the blood supply to the leg seems

to predispose them to recurrence, although the temporary therapeutic response of a group of lesions may be good. Seventy-two per cent. of the patients having an occult or obscure focus of tuberculosis were in the less successful group as regards therapeutic results, while only 28 per cent. of patients of this type make a maximum improvement. When anemia is a prominent feature the internal administration of iron is necessary to secure a marked rise in hemoglobin, the arsphenamine having proved less efficient in this regard.

#### CASE HISTORIES ILLUSTRATING THE TREATMENT DESCRIBED.

CASE 1 (161592).—A girl, aged nineteen years, had been the victim of severe and extensive papulonecrotic lesions with erythema induratum since the age of nine years, associated with a severe tuberculous adenitis and with tuberculous keratitis and severe anemia. Under twenty-four injections of arsphenamine, totalling 10.8 gm., the patient has gained 28 pounds in weight and held it and is practically free of lesions. She had pursued exacting indoor occupation for one and one-half years, and is in excellent general health. She has had one abortive attack of episcleritis since being under observation, but has shown no other manifestations of tuberculosis. Period of observation, two years.

CASE 2 (174923).—A girl, aged twenty-four years, unsuccessfully operated on for tuberculous glands, has had a long history of severe papulonecrotic lesions on the buttocks, thighs and legs and arthritic and myalgic symptoms of such severity as to confine her to bed for weeks at a time. Under sixteen injections of arsphenamine, totalling 6.0 gm., combined with an outdoor regime and nine Coolidge tube exposures, she has gained 20 pounds in weight, maintained it for twenty-two months, has never had a lesion since the first course and now does general housework at home, whereas before treatment she was a semi-invalid.

CASE 3 (200833).—A nurse, aged thirty years, who had been operated on twice for tuberculous cervical adenitis, with only partial success, had a profuse acnitis of the face and ears and a papulonecrotic tuberculid of the forearms. She had received vaccines for acne which made her worse. The eruption vanished before the completion of a five-injection course and at the end of a second additional course of three injections, with a total dosage of 2.6 gm., her complexion was blooming. Her reply to a recent questionnaire states that she has followed only a partial outdoor régime, has gained 7.5 pounds, of which she has held 3 pounds, feels well, has never had a relapse, the glands are palpable and about stationary and she is contemplating Red Cross work.

CASE 4 (212370).—A girl, aged twenty-five years, had been seen by numerous internists and surgeons without a diagnosis having been made. She presented a typical folliclis, with an erythema induratum and papulonecrotic tuberculid. In addition she had a tenosynovitis which had been unsuccessfully operated on and a slight hydrarthrosis of both the ankle and right knee, with marked arthralgic and myalgic pains. A tonsillectomy and appendectomy previously performed had been without effect on the trouble. Ten injections of arsphenamine with an outdoor régime between the two courses resulted in a net gain of 14 pounds in weight, and the total disappearance of all symptoms and signs, including the eruption, the tenosynovitis and the hydrarthrosis by the end of the second course. The patient has been under observation for ten months.

CASE 5 (226884).—A man, aged forty-two years, a barber, who had been unable to work for two years, had an extensive papulonecrotic tuberculid of the legs and trunk and enlarged cervical glands. Under a first course of eight injections of arsphenamine, totalling 3.4 gm., he gained 13.5 pounds in weight, returned to full-time work and has followed no special hygiene. He has subsequently gained an additional 7 pounds. Roentgen ray was not begun until the end of the course, so that the effect must be attributed entirely to the arsphenamine. All cutaneous lesions have disappeared. The glands, while smaller, are still present.

CASE 6 (218528).—An anemic but well-nourished woman, aged twenty-six years, who had lost 40 pounds in weight in four years, presented a papulonecrotic tuberculid of the leg of eighteen months' duration with erythema induratum and a mild secondary anemia without obvious signs of tuberculosis. Under a single course of six injections, totalling 2.4 gm. of arsphenamine, she reports after nine months a gain of 17 pounds in weight and the "wonderful" disappearance of her lesions without signs of recurrence.

CASE 7 (197425).—A girl, aged twenty-one years, of the overweight, florid and blooming type, presented the ulcerative lesions of erythema induratum on both legs, with numerous nodules. She received ten injections of arsphenamine, with a total dosage of 4.1 gm., doing heavy housework sixteen hours a day during the treatment without any special hygiene other than the use of elastic bandages. All the ulcerative lesions disappeared, but nodules occasionally recurred. At the end of fourteen months, in reply to a questionnaire, she reports an improvement of 50 per cent. The lesions are smaller, fewer and less painful than before treatment and last only about a week. She is doing indoor work and sleeps out of doors.

It will be apparent from the discussion and the cases cited that final judgment cannot at this time be passed on the use of arsphenamine either alone or in conjunction with other measures in the management of tuberculids of the papulonecrotic and erythema

induratum types. Only time can establish the permanence of the results. On the other hand, there seems good reason to believe that it has a marked beneficial effect proportional to some extent to the persistence with which it is used and to the total dosage of arspenamine administered. Some of the results produced in the patients longest under observation and treatment have been really remarkable, and failure and lack of improvement can, in a number of instances, be explained by desultory methods. In general, the obese types of patients, and those with occult tuberculosis, offer less outlook for radical improvement than other types, but it is impossible at the present time to generalize or to predict in which case improvement may or may not be expected. When the long duration and the persistence of tuberculids of this type and the heretofore rather dubious results of conventional methods are taken into consideration, I believe the intensive use of arspenamine in conjunction with a régime which treats the underlying cause as well as the symptom deserves to be better known and more extensively employed.

#### SUMMARY.

1. This study deals with a group of 20 cases of various types of papulonecrotic tuberculid and erythema induratum in which arspenamine (Ehrlich "606") was used with good effect in combination with a systemic régime and roentgen therapy.

2. Over half the cases thus treated had demonstrable tuberculosis, usually in the form of a lymphadenitis.

3. Surgical treatment of the lymphadenitis in 9 cases had not demonstrably affected the tuberculid.

4. It would seem from our series that the appearance or the persistence of a cutaneous tuberculid following reasonably complete surgery is an indication for a discontinuance of surgical treatment of the tuberculous focus, and the adoption of a medical means of fortifying the patient against the progress or recurrence of his tuberculous infection.

5. The intravenous administration of arspenamine would seem to afford such a medical means of fortifying the patient's resistance to tuberculosis when combined with an antituberculous hygiene and roentgen ray.

6. Arspenamine offers an excellent means of treating selected cases of obscure tuberculosis as evidenced by the presence of a tuberculid in the absence of a demonstrable focus. Its use in febrile, acute or rapidly progressive cases is not advised.

7. Arspenamine alone is apparently able to produce a striking effect on cutaneous tuberculids. Fifty-three per cent. of 17 cases have been completely cleared of lesions and only 12 per cent. have failed to secure a definite improvement.

8. Arsphenamine is also apparently instrumental in producing a marked constitutional improvement in these cases, evidenced especially by a gain in weight and the disappearance of the "rheumatic" symptoms complained of. Gains of from  $1\frac{1}{2}$  to 40 pounds were registered in our series.

9. The effect of arsphenamine upon the tuberculous adenitis where present is indeterminate, but probably not striking.

10. Roentgenotherapy assists in the reduction of the glands, but we have not found it to compare with arsphenamine in its influence on the general condition or on the cutaneous tuberculid.

11. An outdoor life, forced diet, correction of vascular abnormalities and stasis by elastic support, and careful extirpation of secondary foci of pyogenic infection in tonsils, teeth, etc., are subsidiary but important elements in a successful treatment.

12. These observations are offered as tentative and preliminary, although several of our cases are completing their second year of freedom from lesions and striking general improvement.

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# THE PREVALENCE OF TRICHOMYCES INFECTIONS IN WESTERN NEW YORK, WITH SPECIAL REFERENCE TO *B. FUSIFORMIS*.

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DURING the past eighteen months routine bacteriological findings, including *B. fusiformis* and spirillary filaments, have been so frequent in this locality that I feel justified in making a general report of their clinical distribution, although some of the cases are sufficiently unique to merit separate communications, and for this reason only their salient features will be presented at this time. It is certain that during this period I have encountered such cases with a markedly greater frequency than experienced during a seven-year stay in the University of Michigan. Dr. Lloyd,<sup>1</sup> Medical Director of the Monroe County, N. Y., Sanitarium for Tuberculosis, has over a similar period noted more cases of chronic non-tuberculous pulmonary infection than he has encountered in a number of years' experience in other localities.

Whether their prevalence is representative of conditions in this country cannot be said with certainty at present. The fact that Barker and Miller's<sup>2</sup> paper on the subject is one of the few I have encountered may only mean that other observers have not considered the subject as important. From military sources abroad, however, numerous reports of a high percentage of Vincent's angina cases have appeared, as instanced by the work of Campbell and Dyas,<sup>3</sup> McKinstry,<sup>4</sup> Bouty,<sup>5</sup> Bowman<sup>6</sup> and others quoted by the first-named authors. Perhaps these findings have not extended over a sufficient space of time to designate them as fairly representative, although there is evidence that some organisms of the trichomyces group—notably actinomyces—are particularly common in the soil of western New York.<sup>7</sup> The well-known predilection of the blastomyces and sporothrix infections for the Missouri Valley may be to an extent comparable with the presence of certain members of the trichomyces group in this locality.

The constant association of *B. fusiformis* and spirochetes as the predominating organisms in noma, ulcerative stomatitis, pulmonary

<sup>1</sup> Personal communication.

<sup>2</sup> Jour. Am. Med. Assn., September 7, 1918, p. 793.

<sup>3</sup> Jour. Am. Med. Assn., June 2, 1917, p. 1596.

<sup>4</sup> Practitioner, London, 1917, xcix, 507.

<sup>5</sup> British Med. Jour., 1917, ii, 685.

<sup>6</sup> Proc. Roy. Soc. Med., 1915, ix, Part 2, p. 51; Lancet, London, 1917, ii, 536; British Med. Jour., 1916, i, 373.

<sup>7</sup> Conn. H. J.: Agricultural Experiment Station, Geneva, N. Y., personal communication.



gangrene, putrid bronchitis, gangrenous balanitis, etc., has served to give them etiological significance, although this relationship as well as many points in the biology of these organisms cannot as yet be said to be categorically established, owing chiefly to the rather uniform failure of pure cultures to reproduce the conditions in experimental animals. This phase of the subject which has yielded certain conditional results will not be discussed in this paper.

My attention was first directed to these organisms by a case of generalized streptothricotic infection. One of the commonest conditions encountered has been chronic bronchitis, which frequently was associated with such a foul odor as to merit the designation of putrid bronchitis. Almost invariably these cases have been considered tubercular, owing principally to the duration of the cough, which is usually a matter of several weeks or months, although in one case there is good reason to believe it has existed for fifteen years, covering almost the entire lifetime of the patient. The sputum is usually mucopurulent, and in some of the older cases lymphocytes predominate. Although in certain of the cases, particularly the more acute ones, no difficulty is experienced in finding the organisms, in others they are often restricted to little opaque spherules or grayish-white flakes, which may represent practically pure colonies. In the absence of the tubercle bacillus, assiduous search should be made for these flakes or spherules. They are comparable with the sulphur granules of actinomycotic pus and the caseous masses of tuberculosis, although their consistency is by no means cheesy. From a total of 60 cases, constituting 9 per cent. of our bacteriological examinations, 24, or 40 per cent., have been clinically confused with tuberculosis.

CASE I.—This patient suffered from chronic bronchitis of fifteen years' standing, upon which bronchiectasis and pulmonary fibrosis were superimposed. It followed whooping-cough at two years of age, and some of the best authorities had failed to diagnose it as tuberculous. The sputum contained many of the flakes above mentioned, and when washed were seen to contain a pure culture of a non-acid-fast anaërobic organism, fusiform in shape and decidedly granular, resembling the beaded form of the tubercle bacillus. The patient had a blood count of 20,000 to 25,000 unless she remained relatively inactive. This case, a patient in the service of Dr. J. R. Williams, will later be reported in full.

CASE II.—This case was one of extensive acute bilateral empyema, diagnosed as pneumonia. At autopsy the lungs were negative. The condition was of three weeks' duration, and the last week was characterized by the appearance of mental symptoms suggestive of cerebral involvement. The spinal fluid was very purulent, the condition being one of extensive meningo-encephalitis. The only other finding of note relates to the aortic opening of the heart, whose middle valve was the seat of a friable verrucose excrescence, the

size of a very large pea. Section of this nodule revealed mainly necrotic material, a Gram-Weigert stain of which disclosed myriads of coccoid forms of varying size, and short curved bacillary forms, many of which showed rudimentary branching. From the pus of both lungs and from the spinal fluid the same organism was isolated in pure culture.

Colonies on blood-agar were of medium size, semitransparent or translucent. Microscopically the elements were somewhat pleomorphic; coarse, loosely wavy spiral forms predominated. *Vibrio* forms were also present, some of which were slightly granular at the ends, while others were somewhat club-shaped and granular, resembling diphtheria bacilli. Great variation was noted in the diameter of the different curved forms, some being so slender as to simulate a loosely wavy spirochete. Rudimentary branching was observed. Such forms were found on direct examination of the spinal fluid also. Repeated plating did not show a mixed culture. When first isolated the culture had distinct anaërobic tendencies, but later grew aërobically.

There also occurred 1 case of unilateral empyema and 1 of an acute bronchopneumonia whose sputa were filled with colonies of *B. fusiformis*. Cases III and IV were pleural effusion, one acute and the other chronic. The acute case was of such sudden onset as to have the physical signs of a severe lobar pneumonia, but the characteristic mildness of the clinical symptoms decided the diagnosis in favor of effusion. After withdrawal of 3 quarts of fluid the patient made a rapid recovery. Although 20 c.c. of this fluid were injected into a young guinea-pig, the results were negative. The organism resembled in its general character the one isolated from the case of empyema.

CASE GROUP V. There have been in all 8 cases of Vincent's angina, 6 of the pseudomembranous type and 2 of the ulcerative type. One of the latter has recurred at intervals of two and three months, respectively. Of 2 cases of ulcerative stomatitis, 1 was characterized by the presence of a single large indolent ulcer on the mandible behind the last left molar tooth. The other case was of twenty-five years' duration, characterized by the presence of crops of ulcers, located particularly on the under surface of the tongue and floor of the mouth, but to some extent on the buccal mucosa as well. Occurring in a physician, they came and went without warning and without power for control on his part, until he was finally forced to resign from active practice. The fusospirillary complex was found several times during the past ten years, but was always considered in the light of a secondary invasion. The condition was associated with gingivitis, and one particularly unsanitary crown was present. Removal of the tooth on which it was located revealed myriads of these organisms around its root, one fang of which had suffered necrosis to the extent of half its substance.

CASE GROUP VI.—There were 3 cases of chronic gingivitis, 1 in a boy, aged six years, from very good hygienic environment, was of interest. This child suffered from progressive loss of teeth. The mother said they simply dropped out, one by one, without apparent cause. The appearance of the gums was good, with the exception of a slight dusky hue. No exudate was visible, although a swab passed over the gums revealed rather numerous pus cells and large numbers of long wavy filaments, with a few fusiforms.

CASES VII and VIII.—I have observed 2 cases of pharyngeal and tonsillar mycosis (mycotic pharyngitis). Clinically these cases were characterized by the presence of whitish-yellow cone-shaped elevations attached to the mucosa of the tonsils and their crypts and the pharyngeal wall near the uvula. The adherent quality of these elevations was their most noteworthy characteristic, it being impossible to detach them even with an instrument. Histologically they were characterized by a hyperkeratosis of the mucosa, replacing all but its deepest layer. Between the lamellæ composing these nodules numerous bacillary filamentous forms and cocci were observed.

CASE IX.—This case was one of gangrenous balanitis, the so-called fourth venereal disease. It occurred in a man, aged fifty-five years, starting on the prepuce as a small pimple. From picking it and from irritation in other ways it soon increased in size, and later suppurated. The patient refrained from calling a physician for six months, despite what must have been an alarming increase in its size. When first observed the glans and adjacent body of the penis were about the size of an orange, and where the skin and mucosa were intact the color was very dusky red. A deep, gaping ulcer was eaten out of the swollen glans. The walls of this ulcer were ragged and overhanging, the one from the dorsal surface of the penis projecting in flap-like form, but partially constricted at its base by the phagedenic process. The entire ulcerous portion was deluged in a viscid purulent exudate of foul odor. Microscopically, in addition to numerous cellular elements were myriads of fusiform organisms and long, wavy, slender branching filaments, together with shorter and actively motile spirochetic forms. The blood-culture results will be detailed later. The Wassermann and the complement-fixation reaction for gonorrhea were negative.

CASE X.—This case showed a slow gangrene of the lower extremities, the symptoms taken, as a whole, suggesting Raynaud's disease. The patient gave a history of severe mouth infection four years previously, followed by exacerbations from time to time. The Wassermann reaction was repeatedly negative. Amputation of one leg disclosed a proliferative, obliterating endarteritis in the tibial vessels. Stained with Gram-Weigert there was no lack of pleomorphic, bacillary and coccoid forms positive to Gram, and filamentous and rudimentary branching forms, partially or totally

decolorized. The Levaditi stain for spirochetes was negative. I do not care to draw any conclusions in this case, but the demonstration of this type of organism in the lesions is of note when the pathology rules out Raynaud's disease and syphilis cannot be demonstrated.

CASE XI.—A boy, aged twelve years, developed a slowly progressive painless monarthrititis of the knee-joint, with effusion. No growth was obtained either aerobically or anaerobically from this fluid, but direct examination of the sediment showed granular bacillary forms, some of curved fusiform shape; some coarse solidly staining filaments were also present. Certain of the coccoid forms gave rise to wavy filamentous structures.

Cultures of the tonsils and throat yielded, in addition to the usual cocci, large numbers of long, wavy filaments and diphtheroid forms. Some of the filaments undoubtedly arise from the ends of the diphtheroid or fusiform-like organisms and have a general conformity with those found in the exudate from the knee-joint. A tonsillectomy was followed by recovery of the patient, who has since remained well (six months). It should be noted, in addition, that intravenous injections of foreign protein formed a part of the treatment.

CASE XII.—Another case in point was one of Dupuytren's contracture of fifteen years' standing, which followed streptococcal sepsis from accidental wound infection. For the past five years a slowly progressive general adenitis had developed, and latterly symptoms suggestive of spondylitis. These consisted of spinal rigidity, with pain and tenderness over the spinal muscles and posterior nerve roots. A pure culture of a spirillum was isolated from the tonsillar crypts in practically pure culture, while only an occasional colony of the organism was present on the pharyngeal mucosa. Tonsillectomy in this case has resulted in the immediate disappearance of the spinal symptoms, but has had no effect as yet on the adenitis or the contracture. The patient has gained fifteen pounds in weight, and his capacity for work has been much increased.

CASE XIII.—This case was one of a tumor, slowly progressive in character, which developed in the abdominal wall. Pathological examination revealed a chronic infective granuloma suspiciously tuberculous. Although no specific tubercles or bacilli could be found, the granulomatous tissue was markedly endotheloid in character. The center was broken down, and among the dense, purulent infiltration of leukocytes were large numbers of eosinophiles. A Gram-Weigert stain showed the same type of organism previously described, but in this case the specimen was unfortunately fixed before we had opportunity for a culture of it.

Other cases showing similar findings are briefly: One mastoid abscess ending fatally, organisms recovered in purity (Case XIV) and several of postpartum fever (Case Group XV), in which no

organism could be found in the discharges, but which may have originated from a severe gingivitis, showing fusospirillary organisms (Vincent's), and will be further discussed in connection with the blood-culture results. Organisms of the type under consideration were recovered from one extremely interesting case of toxic hyperchromatic anemia simulating pernicious anemia, arising probably from intestinal ulcers (Case XVI) and a case of unilateral salpingitis, non-gonorrheal in origin (Case XVII).

**RESULTS OF BLOOD CULTURES.** Although for the most part organisms of this character are not found in the blood, in 8 of the 60 cases blood cultures were positive. Cultures were taken in broth and not discarded before the end of ten days, inasmuch as the growth was often slow in appearing. In some cultures it was difficult to determine with certainty whether actual organisms were present, and their relation to the pathological conditions cannot be told with finality at present.

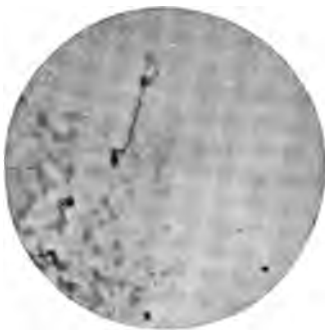


FIG. 1.—Filamentous form occurring in transplant from seventy-two-hour blood culture. In the adjacent triangular coccoid form there are three minute highly refringent areas, peripherally located. Many similar gonidia (?) are found free in the culture. Romanowsky.  $\times 1000$ .

In the culture from a case of gangrenous balanitis a slowly increasing flocculent sediment appeared after three or four days. The best staining results were obtained with the Romanowsky. Cocci and coccoid forms varying greatly in size were found. Many of the cocci had one or more short projections which suggested that actual filaments might so arise. Prolonged search of this culture shows such to be the case (Figs. 1 and 2). In Fig. 1 the short coarser projection arises from a highly refringent area at the periphery of the coccus, which in turn gives off a more slender and somewhat wavy long filament, in the course of which is interpolated another coccus form. Note that the slender filament arises from the side of the coarse projection: (a) From the end of solidly staining filament three faintly staining loops arise. Under certain environmental conditions the filament itself may traverse these loops longitudinally, when

they might be considered as formations homologous to the clubs of the actinomyces.

In Fig. 2, about the middle of the filament, a small oval non-staining body, with fine terminal granules, is present. Similar highly refringent circular bodies, from one to three in number, are found in the cocci and coccoids as well as free in the smear. There is some evidence that they represent gonidia and have to do with the reproduction of the organism. Giant coccus forms, from 3 to 5  $\mu$  in diameter, can also be seen, some of which have several projections, which give them a stellate appearance (Figs. 4 and 5).



FIG. 2.—Note highly refringent oval body in the course of the filament. Romanowsky.  $\times 1000$ .



FIG. 3.—Periplast formation developing about the filament, part of which is marginally located. From the depths of hormone agar. Carbol-fuchsin.  $\times 1000$ .

It is of particular interest in this case that a suspension of these cocci (?) agglutinated the patient's serum in a 1 to 50 dilution, while a normal control in a 1 to 10 dilution was negative. In certain of the other cases, however, no immune reactions were obtained. These cocci may represent a stage in the life-cycle of a filamentous organism. However that may be, it is certain that a hasty examination of this culture would not have shown these filaments in their well-developed form, while their rudimentary form might have been viewed as an artefact. It is to be presumed, at least, that they were related to similar ones seen in the lesion.

In another type of blood culture this diplococcus form is not seen, or if seen, does not grow in transplants under the usual conditions.

In these cases large circular forms predominate, containing usually from two to five oval faintly staining bodies. They may have in addition one or more filamentous projections of varying length. In case the center of the cell is achromatic, the latter spring from well-defined granules located at the periphery of the cell. Cases I, V and XII and one of intermittent fever not discussed here were of this latter type, while the former were represented best by Cases IX, XI and XIV. Cases XVI and XVII were repeatedly negative, which is also true for the remainder of the cases discussed.

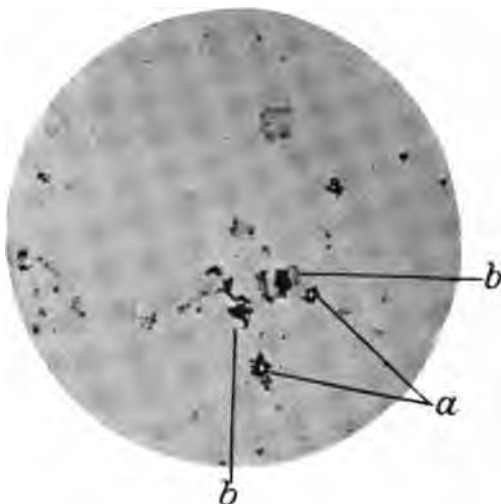


FIG. 4.—Giant coccus forms: (a) early, (b) late. Note development of filament from (b). From a twenty-four-hour hydrocele broth culture, thirty-fifth generation. Romanowsky.  $\times 1000$ .



FIG. 5.—Another giant coccus form, with intracellular light areas and chromatin granules. Romanowsky.  $\times 1500$ .

**RESUMÉ.** In this locality during the past year certain members of the trichomyces group of organisms have been found, with considerable frequency, particularly in pathological conditions of the upper respiratory tract. In certain instances the infection becomes generalized. The most prevalent type of case is a chronic bronchitis

which at times may be of long standing and which may closely simulate tuberculosis. Experimental work is in progress.

The pathological role of *B. fusiformis* and related organisms may be of greater significance than has been supposed. The results of the blood cultures, particularly in cases with positive immune reactions, is suggestive. The presence of filaments in the blood of cases having local infections of this sort must be accounted for and the condition of their growth is such that they may easily be overlooked. An experimental investigation of the bacteriology of one unreported case of undoubted generalized streptothricotic infection suggests that the various kinds of circular bodies found in the blood may be related to the filaments in a cyclic manner. It is probable that some of the cocci grown from the blood are secondary invaders, as it is becoming better established that the latter may invade the organism under a variety of conditions. It would seem, however, that the type shown in the illustrations would not come in this category. The finding of such organisms in mildly febrile puerperal cases in which local uterine signs are negative suggests that the susceptible pregnant state may permit their entrance into the blood from a distant focus of low-grade infection—as, for example, from the mouth. In the few cases we have had their disappearance from the blood was coincident with defervescence.

Metastatic foci may at times arise in these cases and isolation of the organisms in purity be accomplished. This fact, together with their apparent prevalence, does not justify us in regarding them solely as saprophytes.

## THE FACTOR OF SAFETY IN THE PULMONARY CIRCULATION.

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THE excess of pulmonary air space above the actual needs of the individual, as indicated by the astonishingly large proportion of lung tissue frequently found impermeable to air in pneumonia and tuberculosis, has led to numerous experiments to determine the minimum amount of lung substance compatible with life. Da Fano<sup>1</sup> has recently reviewed the literature. Dogs and rabbits appear to have been used exclusively in these experiments. Da Fano and others have removed one lung and found that their animals lived comfortably. Hellin<sup>2</sup> also studied the exchange of carbon dioxide

<sup>1</sup> Virchows Arch., 1912, cvii, 160.

<sup>2</sup> Arch. f. exper. Path. u. Pharmak., 1906, iv, 21.



and oxygen in his one-lunged animals and failed to detect any change from the normal. Courmont<sup>3</sup> removed three-fourths and Bernard, Le Play and Mantoux<sup>4</sup> removed five-sixths of the total lung volume and had their animals survive.

In all of this experimental work emphasis has been laid upon the excess of available air space over the actual necessities of the animal. Little attention, apparently, has been paid to the factor of safety in the pulmonary circulation. Pulmonary circulation and pulmonary ventilation are at least of coördinate importance. Meltzer<sup>5</sup> in his Harvey Society Lecture, discusses specifically only the latter.

An approximate estimation of the factor of safety in the lesser circulation may be arrived at in a number of ways. In the first place the amputation experiments referred to above indicate an excess of vascular space as well as of ventilation. Lichtheim<sup>6</sup> ligated branches of the pulmonary artery and determined the effect upon the systemic arterial pressure. He concluded that from two-thirds to three-fourths of the pulmonary vessels may be occluded without affecting the systemic pressure. This has been confirmed by Tigerstedt<sup>7</sup> and by Gerhardt.<sup>8</sup> Finally, the occlusion of the vessels of the lungs may be induced by the injection of neutral oil into the veins. The results of such an experiment may be estimated (a) by comparing the weight of the animal with the amount of oil necessary to produce a fall in arterial pressure; (b) by roentgen-ray examination of the lungs of animals injected with a suspension of bismuth subnitrate in olive oil; (c) by microscopic examination of sections specially stained for fat.

In a series of experiments reported elsewhere<sup>9</sup> it was shown that approximately 1 c.c. of olive oil for each pound of body weight (2.2 c.c. per kilo) must be injected intravenously in order to induce a permanent fall in arterial pressure in dogs. It was shown, further, that when this "critical quantity" was exceeded even by 2 to 5 c.c. the animal usually succumbed very quickly.

A number of dogs were injected with a suspension of bismuth subnitrate in olive oil. In all of these experiments the animals were under ether anesthesia, the systolic pressure was taken from the carotid artery and the oil-bismuth mixture was injected through a cannula in the femoral vein and washed in with a few cubic centimeters of physiological salt solution. Fig. 1 is a roentgen-ray picture of the lung of a 35-pound dog (No. S 11) which, during a period of one hour and ten minutes, received intravenously 37 c.c. of olive oil-bismuth subnitrate mixture in doses of 2 to 3 c.c. At the begin-

<sup>3</sup> *Compt. rend. Soc. de Biol.*, 1912, lxxiii, 503.

<sup>4</sup> *Jour. de Physiol. et de Path. gen.*, 1913, xv, 16.

<sup>5</sup> *Harvey Society Lectures*, 1906-07, p. 145.

<sup>6</sup> Quoted by Tigerstedt, loc. cit.

<sup>7</sup> *Ergeb. d. Physiol.*, 1903, ii, 554.

<sup>8</sup> *Ztschr. f. klin. Med.*, 1905, iv, 195.

<sup>9</sup> *Simonds, J. P.: Jour. Exper. Med.*, 1918, xxvii, 539.

ning of the experiment the carotid pressure was 165 mm. of mercury. During the hour and ten minutes of oil injections and continuous ether anesthesia the pressure gradually fell to 130 mm. of mercury. The carotid pressure continued to decline slowly and the animal expired one hour later. Postmortem examination showed a moderate dilatation of the right side of the heart, general venous stasis and marked edema of the lungs. The completeness of the injection of the pulmonary vessels is best seen along the margins, where almost every



FIG. 1

vessel of sufficient size to obstruct the rays appears to be filled with the bismuth suspension. This animal lived a full hour with its lungs thus injected.

Fig. 2 is a photomicrograph of a section of lung stained with osmic acid from an 18-pound dog (No. S 17), which received 6 c.c. of olive oil intravenously. The arterial pressure remained unchanged.

Fig. 3 is a photomicrograph of a similarly stained section of lung of a 30-pound dog (No. S 15) injected with 42 c.c. of olive oil in doses of 2 to 3 c.c. During the period of injection (one hour and forty minutes) the blood-pressure fell from 120 mm. of mercury to 100 mm. The animal lived fifty minutes longer, during which

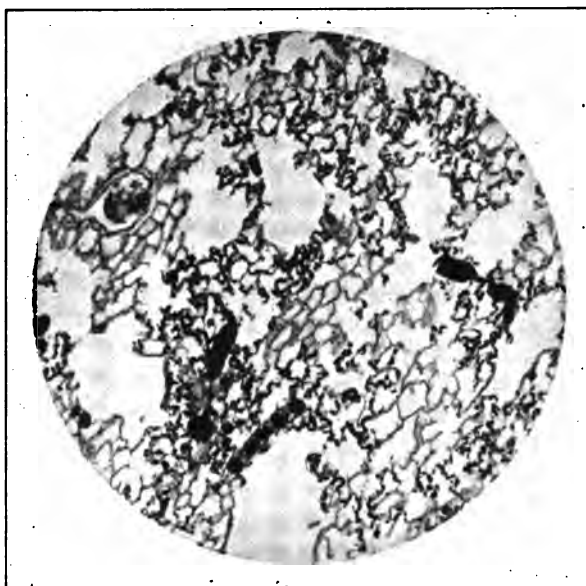


FIG. 2

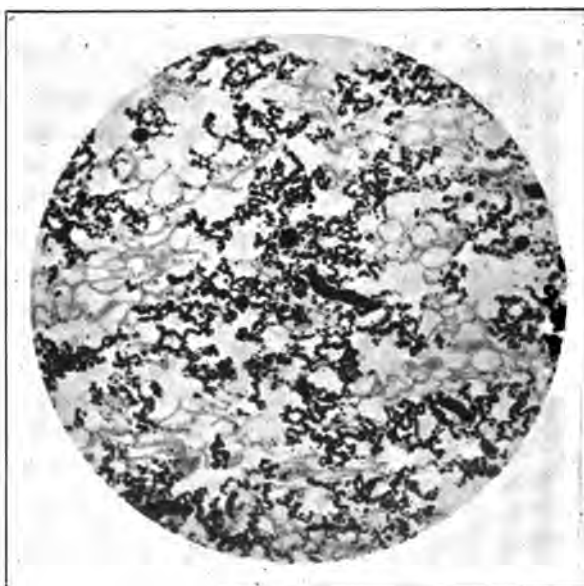


FIG. 3

time the carotid pressure gradually declined. The postmortem examination showed marked dilatation of the right ventricle; the left ventricle contracted and was practically empty; about 40 c.c. of clear fluid was in the pericardial cavity; and there was marked edema of the lungs.

In another series of experiments 0.5 to 0.75 c.c. of sterile olive oil per pound of body weight was injected with aseptic precautions into the saphenous veins of dogs under ether anesthesia. These animals showed no clinical disturbance during the succeeding twenty-four to forty-eight hours except a tendency to dyspnea on exertion. At the end of this time these dogs were again anesthetized and the systolic pressure in the carotid artery taken. It was not found to be below the average for normal dogs.

There are two elements in the factor of safety in the pulmonary circulation. The *primary* element has to do with the pulmonary vessels themselves. In the first place there is evidence that under normal conditions there is present in the lungs a considerable amount of "dead vascular space" in which the vessels are more or less collapsed or in which the blood does not actively circulate. This was the conclusion of Cohnheim and Litten<sup>10</sup> as a result of their attempts to inject the lung through the pulmonary artery. This interpretation appears to have been accepted by Lichtheim<sup>6</sup> and by Tigerstedt.<sup>7</sup> Ghoryeb and Karsner<sup>11</sup> have called attention to the remarkably free anastomosis and early division into capillaries of the pulmonary artery. Finally, and most important, the vessels of the lungs very readily undergo passive dilatation. Their walls are relatively thin and the capillaries in the alveolar walls have little support. The existence of vasomotors in the lungs, as Howell remarks, "has not been demonstrated." The pressure in the pulmonary artery is relatively low, the observed average pressures for dogs collected from the literature by Tigerstedt<sup>7</sup> ranging from 16.9 to 29.6 mm. of mercury. Hence, the dilatation of these vessels is probably purely passive and is dependent upon the volume of blood in the lungs, with or without increase in pressure in the pulmonary artery.

The *secondary* element in the factor of safety in the pulmonary circulation is the readiness with which the right ventricle is able to increase its work and even to hypertrophy when necessary. It may be stated, as a general rule, that any obstruction in the pulmonary circulation of sufficient degree to raise the pressure in the pulmonary artery and of sufficient duration will result in hypertrophy of the right ventricle.

A blocking of any considerable portion of the vascular area of the lungs results, therefore, in (a) an opening up of a part or all of the "dead vascular space;" (b) passive dilatation of the still patent vessels, especially of the capillaries; and (c) an increased pressure in

<sup>10</sup> Virchows Arch., 1875, lxx, 99.

<sup>11</sup> Jour. Exper. Med., 1913, xviii.

the pulmonary artery due to increased energy of the contractions of the right ventricle. As a result of the action of one or all of these elements the amount of blood which reaches the left ventricle is not diminished until the obstruction reaches excessive proportions. It is conceivable, however, that the sudden occlusion of a very large proportion of the vascular area of the lungs, as when a large embolus plugs one of the primary branches of the pulmonary artery, may cause the adaptive mechanism to break down and death rapidly ensue.

The importance of the secondary element in the factor of safety—that is, the ability of the right ventricle to increase its energy of contraction—is shown in the cases of the experiments described above. In Dog No. 17 (Fig. 2) at least one-half of the vessels of the lungs appear to be plugged with droplets of oil, without a fall in arterial blood-pressure. In those animals allowed to live for twenty-four to forty-eight hours after the injection of the oil a still greater proportion of vessels must have been occluded, for the amount of oil per pound of body weight was greater than in the case of Dog No. 17. These animals survived without any reduction of arterial pressure. Dogs No. 11 (Fig. 1) and No. 15 (Fig. 3) had three-fourths or more of the vascular space of their lungs occluded with oil, and yet each survived for an hour after the arterial pressure began to decline. The findings at autopsy indicate that the immediate cause of death in these animals was the failure of the right ventricle, which was always found dilated, and the edema of the lungs. The edema added to the difficulties in two ways: (1) by interfering with ventilation in the already embarrassed lung, and (2) by increasing the viscosity of the blood through loss of fluid. Gauss<sup>13</sup> found that the mere presence of fat droplets in the blood increased its viscosity.

The factor of safety in the pulmonary circulation may have a very practical importance in several ways:

1. It may act as a safety-valve to relieve back pressure in diseases of the left side of the heart. It is thus an essential element in compensation in cardiac diseases. Kuno<sup>13</sup> showed that the blood content of the lungs may vary from 8.8 per cent. to 19.44 per cent. of the total amount of blood in the body. The amount of blood that can be passively stored in the lungs and thus shunted from the general circulation may be as great as 120 per cent. of that normally present in those organs.

2. There is a close relation between the condition of the pulmonary capillaries and the ventilating capacity of the lungs. Peabody<sup>14</sup> has shown that the "pulmonary reserve," that is, the relation between the minute volume of air breathed at rest and the highest minute volume which the patient is capable of breathing, is reduced

<sup>13</sup> Arch. Int. Med., 1916, xviii, 69.

<sup>14</sup> Jour. Physiol., 1917, li, 154.

<sup>15</sup> AM. JOUR. MED. SC., 1917, clv, 100.

in many cases of cardiac disease. "This decreased capacity to breathe deeply may depend upon a change in the elasticity of the lungs which results from an engorgement of the pulmonary vessels. This is in accord with the observation that dyspnea is an earlier manifestation in mitral than in aortic lesions."

3. The factor of safety is responsible for the maintenance of normal systemic blood-pressure in those diseases of the lungs, such as emphysema, chronic interstitial pneumonia, lobar pneumonia and tuberculosis, in which there is an extensive reduction of the total vascular area of the lungs either by destruction or occlusion of large numbers of bloodvessels. It is in this type of cases that the secondary element—namely, increased activity or hypertrophy of the right ventricle, plays an important role; for in practically all of the chronic diseases mentioned above there is some hypertrophy of the right ventricle.

4. It accounts, also, for the difficulty encountered by Mann<sup>15</sup> and others in their attempts to produce fatal experimental pulmonary embolism and for the relative rarity of fatal results in humans following the lodgment of aseptic emboli in the lungs.

It is with pleasure that I acknowledge my obligation to Mr. J. B. Zhingrone, roentgenologist to Mercy Hospital, Chicago, for the accompanying roentgenogram and for numerous others which he kindly prepared in course of these experiments.

<sup>15</sup> Jour. Exper. Med., 1917, xxvi, 387.

## REVIEWS

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**A DIABETIC MANUAL. FOR THE MUTUAL USE OF DOCTOR AND PATIENT.** By ELLIOTT P. JOSLIN, M.D., Assistant Professor of Medicine, Harvard Medical School; Consulting Physician, Boston City Hospital; Collaborator to the Nutrition Laboratory of the Carnegie Institution of Washington in Boston. Pp. 187. Philadelphia and New York: Lea & Febiger.

DR. JOSLIN has given us in this little book a gem of rare value. It is written so that patients of ordinary intelligence can grasp the problems of diabetes and lend intelligent coöperation to the physician attempting to secure for them the maximum safety in health.

Part I gives in untechnical language a rapid survey of the whole subject. Part II retraces with more detail and contains an outline of the treatment of the severer diabetic. Part III contains diet tables and recipes which Dr. Joslin has found valuable in his daily practice; these chapters will prove of great practical value. Part IV gives the simplest tests for the estimation of sugar and acid bodies in the urine, the sugar in the blood and the carbon dioxide in the alveolar air.

Too much can hardly be said in praise of this little volume from the hands of such an eminent authority as Dr. Joslin. C. N. S.

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**THE ORTHOPEDIC TREATMENT OF GUNSHOT INJURIES.** By LEO MAYER, M.D., Instructor in Orthopedic Surgery, New York Postgraduate Medical School and Hospital, with an introduction by Col. E. G. Brackett, M. C. N. A., Director of Military Orthopedic Surgery. Pp. 250; 184 illustrations. Philadelphia and London: W. B. Saunders Company.

ORTHOPEDIC surgery has become of more than ordinary interest since the War on account of the value of this science in the treatment of the mutilating injuries that occur to bones and joints as a result of gunshot wounds. As the author states in his preface, this book is not a treatise on orthopedic surgery, but its purpose is merely to emphasize certain principles and rules of guidance in the treatment of war injuries that have been of value. Treatment is con-

sidered under two main headings: that given at the front and that at the base hospital. Among the many timely subjects presented, the fitting of artificial limbs and the methods of rehabilitation of the wounded are especially well handled. These subjects are most important at this time, and must be of interest to every physician, no matter what line of work he is doing.

F. B. B.

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OXFORD LOOSE-LEAF SURGERY. By VARIOUS AUTHORS. Edited by F. F. BURGHARD, M.S. (LOND.), F.R.C.S. (ENG.), Colonel, A. M. S., Lecturer on Surgery and Surgeon to King's College Hospital, and ALLEN B. KANAVAL, A.B., M.D., F.A.C.S., Lieut. Col., U. S. A., Associate Professor of Surgery, Northwestern University Medical School. In Five Volumes. Volume I. Pp. 971; 354 illustrations. New York: Oxford University Press.

WITH the appearance of the first volume of the *Oxford Surgery* it may be said that a new era has been reached in the publication of surgical books. The idea of loose-leaf books is certainly not new to the commercial world, where the advantages of such a system have long been appreciated on account of the ease of adding or subtracting sections at will; but this is the first time that any elaborate surgical work has been undertaken along these lines. The great objection that has been raised against the investment in surgical books in the past has been that the return hardly justified the expense on account of the ever-changing views on such matters as surgical technic and treatment, not to mention the constant stream of entirely new problems and important discoveries that come to light. A book that is new today is old tomorrow, and in the past it has been necessary for the surgeon to buy a new book each year, at least, in order to get the latest information, which, as a rule, constitutes but a very small part of any volume, the bulk of most books being practically the same from year to year. Such methods of publication may rightly be considered as wasteful and unnecessarily expensive, and for these reasons this new surgery should appeal to all. The idea of the publishers is to present five volumes, each of which will be kept up to the minute by the publication of quarterly supplements and by merely placing each part of the supplement in its appropriate place, removing obsolete subject matter if advisable, the owner always has the "latest edition." The present volume represents the work of fifteen well-known contributors and deals principally with the surgery of the extremities, antisepsis, anesthetics and transfusion. The effect of the war on surgery is evidenced by the excellent chapters dealing with gunshot wounds and the Carrel method of treating infected wounds.



In spite of the fact that practically every part of the book will probably be subject to revision from time to time, the publishers have not constructed the volume in such a way that it has a cheap appearance, as might have been permissible, but the type and paper are most acceptable, while the binding borders on the artistic. Illustrations are furnished in abundance, and are well chosen, with a view toward elucidation of important subjects. This is especially noticeable in that part of the book dealing with the technic of amputations.

F. B. B.

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TEXT-BOOK OF CHEMISTRY. By R. A. WITTHAUS and R. J. E. SCOTT. Seventh edition. Pp. 477. New York: William Wood & Co.

THIS book covers both inorganic and organic chemistry, and also includes some discussion of toxicology. The material is so condensed and abridged, particularly the part dealing with general and inorganic chemistry, that it will be of little use to the student who has not had any previous training in the subject. The discussion of the general principles seems to be especially brief and inadequate. The introductory remarks dealing with physical properties will be useful only to the most elementary student.

Such terms as "disodic" (page 41), and "ethylic" (page 51) are obsolescent, and should have been replaced by "sodium" or "disodium" and "ethyl." Other instances of old-fashioned terminology may be found in the book. The use of the expressions "acidulous elements," "amphoteric elements" and "basylous elements" is not strictly correct, inasmuch as the elements in the free state are neither acidic nor basic. The classification in which these expressions are used is a good one, however.

The portion of the book dealing with organic chemistry is much more thorough and modern than the first part. The impression is gained that this part of the book was much more thoroughly revised than the portion dealing with inorganic chemistry. Here the nomenclature is modern and the formulas are correct. An exception to this is found in the case of muscarin, which is given as a trihydroxy compound instead of the usually accepted aldehyde formula. It is doubtful if muscarin ever results from the putrefaction of protein. Lecithin and similar lipoids are much more likely to be its source.

Since all medical students of today have studied both inorganic and organic chemistry in the regular college course, it is difficult to see how a book of the nature of this one can be of any use to them. The book will be of undoubted use to students of pharmacy and dentistry, and others who find it necessary to cover the entire subject of chemistry in a short time.

B. M. H.

**DISPENSARIES: THEIR MANAGEMENT AND DEVELOPMENT.** By MICHAEL M. DAVIS, JR., PH.D., Director of the Boston Dispensary and ANDREW R. WARNER, M.D., Superintendent of Lakeside Hospital, Cleveland. Pp. 438. New York: The Macmillan Co.

Two of the largest dispensaries in this country are managed respectively by the two authors of this treatise. Their observations, therefore, have peculiar value and ought to be of assistance to all who are striving to meet the medical and social needs of the poor. Chapters of their book are devoted to the history of dispensaries; to the fundamental principles underlying the work of dispensaries; to technic, including consideration of building plans; to special types of dispensaries referring briefly to the pay clinic; and to public problems, including the relationship of the dispensaries and the Medical Profession, efficiency tests and financing. Suggestions for by-laws and rules of a dispensary are given at the end of the book.

Too much praise cannot be given the authors for presenting, with such completeness of detail, the many phases of this most important work. Differences of opinion naturally exist, and unfortunately the tendency of most organizers and administrators of hospitals and dispensaries is to forget that the greater charity is from the hands of the physicians giving their time and energy to medical service for the poor. The humanitarian motive or instinct actuates the physician more than the thought of gaining professional proficiency, a position not appreciated often by financial contributors to dispensaries or those who make their living in such work. Had the authors viewed the situation a little more from this viewpoint a truer presentation would have been made. Of particular interest are the chapters on records and statistics; on follow-up systems; on finance and efficiency tests. The book, as a whole, is a very valuable contribution to the rapidly increasing literature on this subject and with the possible exception of the above-mentioned criticism is all that could be desired.

C. N. S.

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**DISEASES OF THE HEART: THEIR DIAGNOSIS, PROGNOSIS AND TREATMENT BY MODERN METHODS.** By FREDERICK W. PRICE, M.D., F.R.S. (Edin.). Pp. 472. London: Oxford University Press.

ALL physicians of every specialty are concerned regarding the heart, and therefore to all physicians a complete authentic treatise on diseases of the heart will appeal. The above book is from the hands of one eminently qualified to write authoritatively. Dr. Price was for many years associated with Sir James Mackenzie and Professor Cushny, both of world-wide reputation. The chapters

are all written with the very evident intent of being practical and useful, but with detail sufficient to explain all the interpretations. The analyses are all made in the light of studies by means of the clinical polygraph and the electrocardiograph, but there is included an account of such knowledge of the diagnosis, prognosis and treatment of cardiac disorders as was in our possession prior to the introduction of these more recent methods.

Of special interest at this time are the chapters on chronic valvular disease in view of the enormous number of observations made in our own army camps. Some differences of opinion are naturally noted. For instance, Goodman recently observes that in mental stenosis at Camp Jackson the blood-pressure was usually above normal, while Price refers to it as being usually below normal. The chapter on carditis—the rheumatic infection of the heart in childhood—and the chapter on congenital heart disease are exceptionally well written.

The book ends with an excellent chapter on clinical electrocardiography, which is described as clearly and fully as the reviewer has seen anywhere.

C. N. S.

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COMPENDIUM OF HISTOPATHOLOGICAL TECHNIC. By EMMA H. ADLER, formerly Technician in the Pathological Laboratory of the Presbyterian Hospital of New York. Pp. 92. New York: Paul B. Hoeber.

THIS little book modestly aspires to supply the student untrained in laboratory work with a brief and handy account of histological technic, and serves this purpose in an admirable manner. The directions are clear and the text and formulas quite free of errors; the work is well adapted for the beginner, but may be improved upon by including interleaves for notes.

J. A. K.

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A MANUAL OF GYNECOLOGY. By JOHN COOKE HIRST, M.D., Associate in Obstetrics, University of Pennsylvania. Pp. 466; 175 illustrations. Philadelphia and London: W. B. Saunders Company.

It can hardly be said there is a scarcity of works on gynecology, but very often, in spite of the possession of several books on this subject, the student, as well as the practitioner, finds it difficult to get the information he wants quickly. This presentation of Dr. Hirst's has been prepared for the purpose of giving the medical student a concise and accurate outline of the subject without the need of voluminous reading. The author's many years of experience in undergraduate instruction renders him peculiarly fitted to fulfil this mission, as it is only by close and intimate contact with

students that one can grasp their needs. The book, though small, contains practically all the essential matter that any of the larger books contain, and is thoroughly up to date. It will undoubtedly appeal to students on account of the didactic manner in which most of the subjects are written, but it is doubtful whether it will enjoy much popularity among practitioners, as it presents very little in the way of that personal element which most physicians require of a new book. Special chapters have been devoted to abnormalities of menstruation and leucorrhea, and although criticism may be directed against the discussion and treatment of mere symptoms, from a practical standpoint these chapters will often be of considerable use to the young practitioner in cases in which it is advisable to temporize. The chapter on cystoscopic technic might have been omitted, as it has obviously no place in a book of this kind. Radiotherapy and endocrinology are reviewed briefly but sufficiently to give the student the most recent accepted facts on these subjects.

F. B. B.

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VACCINES AND SERA IN MILITARY AND CIVILIAN PRACTICE. By A. GEOFFREY SHERA, B.A., M.D., B.C. (Cantab.), Clinical Pathologist to the British Red Cross Hospital, Netley. With an Introduction by Sir CLIFFORD ALLBUTT, K.C.B., M.D., F.R.S., Regius Professor of Physic, University of Cambridge. Pp. 226. London: Henry Frowde and Hodder & Stoughton.

THIS pocket manual aims to record the author's experience with vaccines and sera in military and civilian practice, and evidently, according to the text, his experience has been very satisfactory, especially with vaccines; he has aimed "to furnish an answer of some kind to those who are trying to discredit and discourage specific therapy" and to render his work of material use to general practitioners. The book is written in a simple and semipopular style, is generally good, and probably fulfils, in large measure, the aims of the author. Vaccines have received particular attention in the prophylaxis and treatment of a wide variety of infections, including wounds, and covers about 120 pages; the author is particularly impressed with the efficacy of autogenous vaccines and generally decries the use of stock commercial products. The therapeutic use of the tuberculins is condemned as being neither justified by use nor supported by experimental evidence. Minor errors are occasionally found; one is surprised to read on page 19 that the "toxin" of anaphylaxis is elaborated by the liver, and the term "parasymphilis" (page 191) is now generally regarded as obsolete. Sir Clifford Allbutt has contributed an interesting introduction, and expresses his belief that in vaccination great possibilities lie hidden and that failures occur largely because we are as yet far from understanding the use of the weapon. J. A. K.

**TUMORS, INNOCENT AND MALIGNANT: THEIR CLINICAL CHARACTERS AND APPROPRIATE TREATMENT.** By SIR JOHN BLAND-SUTTON, LL.D., F.R.C.S., Surgeon to and Chairman of the Cancer Investigation Committee of the Middlesex Hospital, etc. Sixth edition. Pp. 790; 383 illustrations. New York City: Paul B. Hoeber.

THE appearance of a sixth edition of this book indicates that in spite of its rather limited, though none the less important scope, it continues as one of the standard works of its kind. There are evidences of a revision throughout and a few new chapters have been added. The author's views concerning the relation of septic organisms to cancer seem a bit dogmatic, and to state that the degree of malignancy of a tumor varies directly as its exposure to pathogenic organisms needs more proof than has been presented. The use of radium in the treatment of neoplasms is mentioned, but no enthusiasm is exhibited over the results to be attained. In number the illustrations are sufficient; in style they belong to the books of a few decades ago, when wood-cut illustrations were all that could be desired.

F. B. B.

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**PATHOLOGICAL TECHNIC. A PRACTICAL MANUAL FOR WORKERS IN PATHOLOGICAL HISTOLOGY AND BACTERIOLOGY.** By F. B. MALLORY, M.D., Associate Professor of Pathology, Harvard Medical School, and J. B. WRIGHT, M.D., Pathologist to the Massachusetts General Hospital. Seventh edition, revised and enlarged. Pp. 555; 181 illustrations. Philadelphia and London: W. B. Saunders Company.

THAT this book has reached the seventh edition is proof of its popularity and that it amply fulfils the designs of the authors as a book for practical use in pathological laboratories, both as a guide to beginners and as a source of reference for the advanced; indeed, but few laboratories are without a copy of Mallory and Wright.

In this edition the authors have added much new matter scattered throughout the book, but the reviewer was surprised to find that no mention has been made of a technic for determining the hydrogen ion concentration of culture media which is supplanting the older methods of titration; likewise, he believes that the authors should include a description of the preparation of normal and decinormal solutions of sodium hydroxide and hydrochloric acid. The section on postmortem technic could be improved upon by including more illustrations, while the chapters on clinical pathology and serological technic should either be made more complete or omitted altogether, yielding more space for descriptions of bacteriological technic.

The pages of the present volume are smaller in size than in the former editions, rendering the book compact and handy; the text is clear and maintains the high order of general excellence and usefulness of this well-known work.

J. A. K.

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**SYMPTOMS AND THEIR INTERPRETATION.** By JAMES MACKENZIE, Lecturer on Cardiac Research, London Hospital. Third edition. Pp. 318; 19 illustrations. New York: Paul B. Hoeber, 1919.

THE two appendices, added in this the third edition, deal with topics quite in accord with the point of view and subject-matter of the book itself. In one is a summary of a surgeon's study of hyperalgesic points in several series of abdominal cases which came to operation. This independent study corroborates certain of the author's conclusions regarding the reflex symptoms of visceral disease and exemplifies the value of the line of study of symptoms laid down in this book. In the other the author gives suggestions to those who have asked for guidance in matters of research in clinical medicine. These suggestions are very characteristic of the author's outlook, resulting, as they do, from his own experience. In the first place he evidently considers research in clinical medicine to be the most difficult of all varieties of medical research, because of the large background of experience which it requires. At any rate, he thinks that only those are fitted who have discovered their problem for themselves, and this must come in the ripeness of experience. The field which he believes open to the general practitioner above all others is the study of the early stages of diseases, the prehospital stage, where the subjective symptoms are apparent to the patient, but the signs indefinite or undetectable to the observer. The correlation of these earliest symptoms with the later course of the disease would lead to an increase in our knowledge which would tend to earlier diagnosis and more efficient early treatment. These and other suggestions add a new feature of interest to this original and stimulating book.

W. H. F. A.

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**STUDIES IN THE ANATOMY AND SURGERY OF THE NOSE AND EAR.** By ADAM SMITH, M.D., Past Instructor in Operative Surgery, Columbia University Medical College. Pp. 157; 45 illustrations. New York: Paul B. Hoeber.

THE anatomical basis of the present volume is constituted principally by a series of frontal and sagittal sections of the entire head,

which have been selected as showing to advantage structural relationships of importance in treatment, surgical or otherwise. These sections are shown in full-page plates, with descriptive text on the opposite pages, in the manner of an atlas. This part of the book forms Chapter III, a contribution to the anatomy and surgery of the nose and its sinuses. Such sections are always interesting and instructive, and the illustrations portray these for the most part in clear diagrammatic form. Some areas of the sections are left, however, quite undeciphered, perhaps intentionally, but it is a little unfortunate that the artist did not use a more distinctive technic for the various constituent tissues in some localities, as in the portrayal of uvula, inferior turbinate and tongue in Plate XI. Also, in some places, minor distortions incidental to the preparation of the sections have not been rectified before the artist began his work, and these naturally do not aid in a clear understanding of the normal relations. For the main points which the author emphasizes, however, the illustrations are entirely adequate. Other chapters treat of nasal breathing, treatment of intranasal conditions, removal of the pituitary gland, postural treatment of otitis media and mastoiditis and anatomy and surgery of the temporal bone. In these the author elucidates many points in treatment in which he inculcates constantly the lesson on the importance of a thorough knowledge of the anatomical relations. In making clear this method of procedure the author has been most successful, and the book must be regarded as a helpful addition to the literature. W. A.

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NEOPLASTIC DISEASES. A TEXT-BOOK ON TUMORS. By JAMES EWING, M.D., Sc.D., Professor of Pathology, Cornell University Medical College, New York City. Pp. 1027; 479 illustrations. Philadelphia and London: W. B. Saunders Company, 1919.

THE demand for books which are solely devoted to such a special subject as oncology has not been very great in the past, and, as a result, there have been comparatively few works of this kind presented, especially by American investigators. During recent years however, there has been considerable interest shown in neoplastic diseases, more especially the malignant types, and many masterly monographs have appeared from American laboratories and clinics. The time is ripe, therefore, for the appearance of an exhaustive collective review, as it were, which will place before the English-speaking profession all that is known about these most interesting pathological processes, giving due credit to all who have been earnestly working in this special field.

Upon critical analysis we find this book divided into two main sections: one dealing with general and one with special oncology.

The section on general oncology begins with a most interesting and complete as well as highly instructive chapter on the historical phase of the literature on tumors, the references dating as far back as 1500 B.C. The various theories concerning the etiology of neoplasms are presented at length and ably discussed, and a most complete chapter on experimental cancer research forms a very valuable section. Under special oncology the various organs and regions of the body are considered as affected by neoplastic formations. Each chapter in this section may truly be considered a monograph by itself. Naturally the treatment of these conditions is not an important part of this book, but under each disease enough treatment and prognosis are discussed to give the reader a more than ordinary insight into the latest views of the profession. A glance at the lengthy bibliography that is given at the end of the book will suffice to impress the reader with the enormous amount of labor that has been expended in the preparation of the book, and, moreover, it presents in concise form a wonderful index to the world literature for those that care to go even further into the subject than the author has gone. The author is to be congratulated upon the enormous amount of material and statistical data that he has been able to gather into this one volume, and it can reasonably be expected that this work will be freely used and quoted in the future by numerous contributors to scientific literature.

Without any desire on the part of the reviewer to be hypercritical, mention must be made of the absence of a chapter dealing with tumors of the umbilicus. Although such growths are comparatively rare and unimportant, in the light of Cullen's recent monograph a short discussion, at least, should have been included in this otherwise excellent book. The subject-matter is amply illustrated with photographs of the clinical appearance of the various neoplasms as well as with many beautiful photomicrographs. While the work is essentially one on pathology, as stated before, it contains so much practical information on the clinical course of these diseases that it will be of unlimited use to the scientific practitioner. F. B. B.

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PRINCIPLES AND PRACTICE OF OBSTETRICS. By JOSEPH B. DELEE, A.M., M.D., Professor of Obstetrics at the Northwestern University Medical School. Third edition. Pp. 1089; 949 illustrations. Philadelphia and London: W. B. Saunders Company.

THIS book needs no introduction to the profession, since it became one of the foremost works on obstetrics as soon as it was published. The author was particularly fortunate in being able to obtain foreign literature throughout the war, and he has used it to good advantage in the present edition. The book is slightly larger than the previous



editions, due to the addition of new material in connection with operative procedures and anesthesia as used in obstetrics. The author has never been a great advocate of "twilight sleep," and his views on this subject have not been changed in the light of more recent experience. Nitrous oxide and oxygen anesthesia have been useful, but the administration must be under the direction of an expert anesthetist. The general high standard of the previous editions has not only been maintained, but additions, revisions and corrections have been made wherever such changes have been necessary. The reviewer would find it difficult to criticise other than favorably such a masterly volume. F. B. B.

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EQUILIBRIUM AND VERTIGO. By ISAAC H. JONES, M.A., M.D., Instructor in Neuro-otology, University of Pennsylvania Medical School: With an Analysis of Pathological Cases. By LEWIS FISHER, M.D., Laryngologist and Otolologist, Mt. Sinai Hospital, Philadelphia. Adopted as Standard for Medical Division, Signal Corps, Aviation Section. By Surgeon-General and Chief Signal Officer, U. S. Army. Pp. 444; 130 illustrations. Publisher: J. B. Lippincott Company, 1918.

SINCE the announcement of Bárány's very important studies of the static labyrinth, quite a number of years ago now, we have been waiting with a great deal of impatience for the appearance of an ably written text-book on this subject. We are perfectly conscious of the excellent publications of Friesner and Braun: one on the "Labyrinth" and the other on "Cerebellar Abscess," and would like to take this opportunity of expressing our high opinion of these works. Nevertheless, the subject of "Equilibrium and Vertigo" is for the first time being treated in its entirety in this publication of Jones, which we, therefore, welcome with enthusiasm as a very important addition to medical literature. The author has succeeded in presenting a complex subject in a very simple and at the same time comprehensive manner, and by the very free use of pictures and diagrams, backed by a very clear style of writing, has cleared away unimportant details and put forward the important facts which are necessary in making accurate diagnoses.

The book is divided into two parts: the first part dealing with the practical uses of a study of the internal ear, and the second part being devoted to the real study of the internal ear itself and its ramifying connections. We might perhaps divide off the last chapter into a third part, as it consists of a series of pathological cases very beautifully written up and analyzed by Dr. Lewis Fisher, and is a very important and instructive addition to the book. Some 240 pages are devoted to this chapter.

The first nine chapters, making up the first section of the book, could be read with advantage by every general practitioner, as they put forth very forcibly the importance of the internal ear in its relation to certain general disturbances, which unless this relationship is understood cannot be properly diagnosed and treated. Perhaps the author's enthusiasm will give one who gets his first knowledge of the internal ear mechanism from a reading of these chapters the feeling that the writer believes the summit of neurological diagnosis has been reached. We rejoice in this impression, and though the summit may not be reached, we are much higher up the ladder since the recognition of the importance of the kinetic-static labyrinth. We must, however, criticise the statement of the author that seasickness results from overstimulation of the semicircular canals. Unquestionably, the internal ear is responsible for this disturbance, but it is due to the stimulation of the maculæ of the utricle and saccule rather than of the semicircular canals. The absence of nystagmus and sensations of turning in seasick persons seems to us to prove the above statement. On the whole, however, there is very little adverse criticism that can be properly made. It is a fine text-book. The illustrations are numerous, and, what is important, also instructive. We might wish that the captions were a little more descriptive, especially those dealing with the anatomy. The use of reproductions from moving-picture films is a new idea, and though they seem to take up a lot of room, really convey the phenomena of past-pointing, etc., better than any other method of illustration known to us. The majority of the anatomical illustrations are stereoscopic photographs.

G. B. W.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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**A Report on Goitre among Draft Men from the Northwest.**—BRANDEL and HELM (*Arch. Int. Med.*, January, 1919, No. 1, vol. xxiii) state that during the May and June examinations of Western drafted men at Fort McDowell, California, a remarkable number of thyroid enlargements were noticed. Many were unassociated with toxic symptoms. A considerable proportion, however, had true hyperthyroidism and were unfit for general military service. As a result of their observations the authors conclude that goitre is more common in young men than the experience of the general practitioner would suggest. There are definite goitre districts in Oregon, Montana and probably in Nevada. Locality appears to be much greater in importance than family tendency. Many of the goitres in draft men are unmistakably toxic and should be a cause for rejection. The more toxic cases show a tendency to nephritis in addition to the classical cardiac symptoms. The authors believe that all men having thyroid enlargement should be examined systematically for evidence of cardio-renal pathology.

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**Non-specific Therapy in Arthritis and Infection.**—BRANDEL and HELM (*Arch. Int. Med.*, January, 1919, No. 1, vol. xxiii) report a study of the changes in the blood consequent on the intravenous injection of typhoid protein, when the analogy between the typhoid paroxysm and the malarial paroxysm was considered. The typical reaction following the injection of a foreign protein is characterized

by chilliness or a definite chill, fever, pain, sweating and characteristic changes in the form elements of the blood. A leukopenia followed by leukocytosis was sometimes of very marked degree. The authors studied a series of ten cases. These are reported in detail and graphically illustrated by charts and tables. They conclude that the intravenous injection of typhoid protein (vaccine) almost invariably initiates a leukopenia, followed by a leukocytosis which is associated with but not necessarily proportional to the pyogenic reaction. The induced leukocytosis is chiefly polymorphonuclear, even in those cases in which there is an initial lymphocyte increase. Atypical cell forms, particularly in the lymphocyte group, occurs. Accompanying these there are nucleated reds and myelocytes. The authors believe that during the leukopenic stage polynuclears leave the blood stream and enter the tissues; that the subsequent increase in cells is due to an overproduction of cells from the respective mesenchymal fundaments, as is witnessed by the presence of myelocytes and nucleated cells. The temperature reaction and the clinical findings are not in the nature of an anaphylactic response, as is shown by the absence of eosinophilia. The cyanosis observed is not due to methemoglobin. Improvement is most marked following those reactions in which there is a good myelocytic response. This is probably a measure of the capacity of the body to react. It is believed that dead protein is the common etiological factor, that typhoid protein paroxysm, like the malarial paroxysm, is due not to the presence of new organisms but to the death of the old ones.

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**Epidemic of Cerebrospinal Meningitis.** — CAMAC and BOWMAN (*Arch. Int. Med.*, January, 1919), from observations made at General Hospital No. 6, Fort McPherson, Ga., found that in the winter of 1917 and 1918, cases show no uniformity of symptoms or signs. The most uniform, however, were headache, 100 per cent.; fever, 80 per cent.; delirium, 60 per cent.; vomiting, 60 per cent.; Kernig, 50 per cent.; episthotonos, 30 per cent.; orthotonos, 20 per cent.; but no cases presented the hemorrhagic spinal spotted rash, but possibly the early administration of serum prevented this widespread toxic effect. Although this may be possible, the reviewer has seen epidemics before the serum treatment was commonly used in which spots were only rarely present and in which the symptoms were so varied and misleading that patients were admitted to all the different services of a large general hospital, cases being mistaken for appendicitis, when abdominal symptoms predominated, for uremia, eclampsia, pneumonia and various other conditions. In two of the cases there were no signs except fever and delirium. Early diagnosis is of the greatest importance and in many cases this is only possible by lumbar puncture and examination of the spinal fluid. It is particularly important that this should be done in cases of fever and delirium with no other physical signs, and that one should have everything ready to administer the serum. If the spinal fluid is cloudy or is clear, with physical signs of meningeal involvement, give 20 to 30 c.c. of antimeningococcus serum. Two such treatments should be given every twenty-four hours for the first few days and decrease as the patient improves physically. If the patient shows marked toxic symptoms or is doing

badly, intravenous treatment should be tried; 50 to 60 c.c. as often as once every twenty-four hours. This may be followed by rise in temperature to 103° or even 105°, and commonly by chill, but this is often followed by drop to normal or even subnormal, and should cause no alarm. Herrick has reported successful use of intravenous meningococcus serum at Camp Jackson in certain instances. Intravenous treatment should bring favorable results when intraspinal method seems to fail. The temperature is of practically no value as a guide as to when serum therapy should be discontinued. The most reliable guides are the spinal fluid and the general condition of the patient. The spinal fluid should be clear and free from meningococci. The patient should be clearly in much better condition and free from delirium and toxic signs.

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## SURGERY

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UNDER THE CHARGE OF

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**Repair of Large Gaps in Peripheral Nerves by Neuroplasty.**—MACKENZIE (*Surg., Gynec. and Obst.*, 1918, xxvii, 353) says the object of his study was three cases which illustrate the utilization of nerve flaps of both central and peripheral origin in order to bridge unusually large gaps in peripheral nerves. He concludes that regeneration and recovery of function are promoted by the use of nerve flaps and that both central and peripheral flaps can be used for such purposes. A peripheral flap by laying down a nerve path may promote regeneration over a great gap; in one case quoted regeneration occurred over a gap of ten and three-quarter inches. The approximation of nerves and their repair should be done in all cases with the least possible delay. (This would apply as well to cases which are infected as to clean cases.) The arrest of trophic shock can be promoted by early closure of large gaps by flaps. Unimpaired nerve tissue should always be utilized for the effective repair of damaged nerves. In their repair, nerves can be successfully sequestered in muscular tissue, so as to promote their own regeneration and that of the muscles in which they are embedded. The principle of sequestration (burial in or covering over by muscular tissue) can be utilized in proper cases so as to avoid infected zones in wounds and also scars and other obstacles to nerve repair. The theory has been held for a number of years past that regeneration can only take place from the central end of a nerve, and more recent studies would tend to confirm this principle. That regeneration on a colossal scale can take place, and has taken place, under conditions in which flaps taken from the peripheral ends of a

divided nerve and utilized to bridge a gap ten and three-quarter inches in length and fixed to the central end of the divided nerve, and that they were successful in restoring motion and power to muscles completely paralyzed by the trauma, is manifest in view of the results obtained in the case referred to above and listed as follows: (1) Trophic recovery is practically complete. (2) There has been recovery in a limited degree of protopathic and epicritic sensibility. (3) There is almost universal recovery of deep sensation. (4) Recovery has taken place of motion and power in groups of muscles which, after the excision of the nerve, were reduced to a hopeless state: (a) The flexor group in the thigh, viz., complete recovery of the semimembranosus, semitendinosus and the biceps; (b) the flexor group in the leg, viz., the gastrocnemius, plantaris, soleus and popliteus. Extensive recovery has taken place in this group which has been progressive; (c) the extensors and flexors in the phalanges and foot. (5) The relatively small and contracted area of absolute cutaneous analgesia. (6) The relatively small area of thermic analgesia. (7) The direct sensibility of the nerve to deep pressure and the transmission of painful sensibility thereby to the foot. (8) Possession of muscular sense. (9) Independent and unaided locomotion; the man can not only walk long distances but can run at considerable rate of speed.

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**Lesions of the Sacro-iliac Joint.**—COFIELD (*Am. Jour. Orthop. Surg.*, 1918, xvi, 418) says that a careful study of the anatomy and functions of the sacro-iliac joints precludes the possibility of subluxation or relaxation occurring except in severe crushing injuries or possibly during the later stages of pregnancy, when all pelvic ligaments are in a state of temporary relaxation. The symptoms occurring in acute and chronic sacro-iliac lesions, as well as many of the sciaticas, are to be explained by sprains of the joint, the spasmodic action of the posterior musculature of the body and the sequelæ resulting therefrom. Manipulation for the cure of sacro-iliac lesions has in the past been practised by the average physician in a purely empirical way, realizing that it was of service in a certain number of cases. On account of the frequent occurrence of anomalies of the spine and pelvis in this region, a roentgen-ray examination can only be of positive value when checked up by a subsequent examination after a cure has been effected. Traumatic lesions of the lumbosacral articulation may simulate very closely those of the sacro-iliac joint and may require a similar method of treatment.

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**Roentgenological Aspects of Hour-glass Stomach.**—CARMAN (*Surg., Gynec. and Obst.*, 1918, xxvii, 426) says that hour-glass stomach should not be considered a disease entity but an end-result of various pathological processes, gastric and perigastric. The possibility of congenital hour-glass stomach must be admitted, although most cases reported must be questioned. The roentgenogram usually shows a much deeper constriction than is seen at operation, due to the fact that the organic narrowing is exaggerated by the spasm. Cases of spasmodic hour-glass, whether intrinsic or extrinsic in cause, are not seen by the surgeon, because they are relaxed by the narcosis. Therefore, if the hour-glass is the only roentgen sign present, the first thing to do is to

exclude extrinsic causes. Belladonna or atropin does not differentiate between the organic and intrinsic types of spasmodic hour-glass stomach. Belladonna to physiological effect will differentiate between the intrinsic and extrinsic types of spasmodic hour-glass stomach. Operations have proved the organic type the most common. However, the spasmodic, when intrinsic in origin, is just as important from the diagnostic standpoint as the organic. The varieties of hour-glass stomach, therefore, admit of the following subdivisions: Congenital and Acquired: (1) Organic: constriction due to structural changes in or about the stomach. Causes: ulcer, scar of healed ulcer, perigastric adhesions, cancer, syphilis, corrosive, resection, gastrotomy, congenital? (2) Spasmodic (or functional): Cramp of the gastric muscle without structural change. Two types: (a) intrinsic; cramp directly produced by lesions in the stomach; causes practically the same as those of organic hour-glass; (b) extrinsic; cramp indirectly produced by causes outside of the stomach: duodenal ulcer, diseases of the gall-bladder, disease of the appendix, neuroses, tabes, lead intoxication, morphin, nicotin; (c) pseudo-hour-glass; simulating the hour-glass form without either spasm or structural change in the stomach; causes: contraction of the abdominal muscles, pressure of stomach against the spine, tumors outside of the stomach, atonic stomach, gas and fecal matter in the bowel.

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**Temporary Internal Fixation of Compound Fractures.**—BROWN and BROWN (*Surg., Gynec. and Obst.*, 1919, xxvii, 440) says that, as a result of our war experience, there is more and more stress being laid upon the mechanical cleansing and immobilization than any other two features in the treatment of fractures. Their experience for the past two years has added what they believe to be as important, or possibly more important, and that is the temporary fixation of the fracture, preferably with the Parham-Martin band, or if not feasible, with a Lane plate; this fixation to be removed under local anesthesia at the end of five or six weeks. The internal fixation frequently reduces or solves the problem of extension. They believe that temporary internal fixation of compound fractures should be more frequently used and that it will prevent many of the difficult reparative operations which we have to do on non-union compound fractures. The incidence of infection is not increased but reduced in direct proportion to the fixation. The bands or plates should never be used with the understanding or hope that they will remain permanently. They prevent excessive deformity and relieve pain between and during the dressings. The Parham band is much to be preferred to the Lane plate, where it can be used, because in oblique and comminuted fractures it is a better mechanical support and brings all the fragments into perfect apposition and does not open the medullary cavity with the possibility of infection and osteoporosis. As complete external immobilization should be maintained as would be if internal fixation were not used.

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**Empyema.**—ROCKEY (*Military Surgeon*, 1918, xliii, 384) studied this subject in connection with his experience at Camp Lewis. Forty-eight cases were operated on; 2 were diagnosed antemortem but not

operated on; 8 were diagnosed only at postmortem; 10 cases of pneumococcus empyema were operated on by rib resection and all 10 were operated on for empyema following measles and 6 recovered; 20 cases of hemolytic streptococcus empyema had only rib resection treatment and 5 died, while 17 more of the same kind had thoracotomy with constant negative pressure treatment and none of them died. The latter is therefore considered the most efficient treatment for the streptococcus empyema. This is shown by: (a) absence of mortality; (b) smooth postoperative convalescence, except in cases of too early removal of drainage tubes; (c) absence of pneumothorax, as proved by the roentgen ray; (d) economy of material and labor.

**Empyema at Camp Custer.**—The Empyema Board of the Base Hospital (*Review of War Surgery and Medicine*, 1918, No. 9, i, 1) summarizes a very illuminating report as follows: In the majority of cases of empyema, a streptococcus has been the causative organism. When grown on blood agar it has been shown to be hemolytic in a large percentage. During the prevalence of empyema, streptococci were demonstrable in a majority of throats of healthy soldiers (including fresh recruits) as well as of patients entering the hospital with respiratory infections. The clinical manifestations include rapid and profound toxemia, the quick formation in many cases of large amounts of pleural exudate and a marked tendency to pocket formation by old and new adhesions in atypical locations. The mortality was highest (61.5 per cent.) in the cases of empyema following measles, lowest (22.7 per cent.) in the cases in which empyema was the primary condition. (Cases following measles not designated primary.) In empyema complicating pneumonia, the mortality was 38.2 per cent.; the mortality of all cases of empyema was 4.5 per cent. At autopsy the outstanding features have been the finding of widespread lesions, with a tendency to involve serous membranes, the occurrence of a severe bronchitis in a majority of cases and a type of bronchopneumonia so distributed as often to resemble a lobar process. Early recognition is important, especially in the acute fulminating types of cases. The diagnosis depends upon close attention to clinical progress, frequent observations accurately made and recorded, and proper interpretation of physical signs. Dulness, the sense of resistance on percussion and the diminution or absence of tactile fremitus are the most reliable signs. The relative incidence of empyema complicating pneumonia was high, one month 50 per cent. of pneumonia cases developing pneumonia. Of 830 cases of measles (including German measles), 4.4 per cent. developed a chest complication of pneumonia or empyema; of this group, empyema was the primary condition clinically in 70 per cent. of cases. The treatment instituted should depend upon the conditions existing in each individual case. No one type of operative procedure should be employed as a routine procedure. Thorough drainage without pneumothorax if possible and with minimum operative procedure seems to be indicated in the acute stage of the fulminating cases. In the cases treated by more radical operation the best results have been obtained by the use of the Carrell-Dakin technic early instituted.



## THERAPEUTICS

UNDER THE CHARGE OF

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**The Treatment of Severe and Progressive Hemorrhage by Intravenous Injections.**—PENFIELD (*Am. Jour. Physiol.*, 1919, xlviii, 121). The blood-pressure of experimental animals was kept at a shock level for various lengths of time by progressive bleeding so that their condition resembled that which must frequently exist in wounded men at the front who have sustained severe and continued loss of blood. After analyzing the condition of these experimental animals according to the duration of low blood-pressure, the amount of blood lost and the degree of acidosis resulting, the author was not able to show that gum-sodium bicarbonate solution or gum-glucose solution is more efficacious in saving life than is an isotonic solution of sodium chloride. By perfusing an isolated vascular bed the author showed that following a large hemorrhage there is a primary constriction of the peripheral vessels. With continued low blood-pressure this constriction passes off and dilatation supervenes. Associated with this dilatation the venous pressure rises while the arterial pressure is falling. All dogs in which the venous pressure rose while the arterial pressure was falling, for a period of twenty minutes or more, died regardless of treatment. The effects of stimulation of the saphenous nerve while these animals were in a condition of profound shock indicated that the reflexes affecting respiration and blood-pressure were not paralyzed, although the author considers that this point deserves more careful investigation.

**The Output of Epinephrin in Shock.**—STEWART AND ROGOFF (*Am. Jour. Physiol.*, 1919, xlviii, 22) found that the rate of output of epinephrin in dogs and cats, after the blood-pressure had been permanently lowered by exposure and manipulation of the intestines, by partial occlusion of the inferior vena cava, by hemorrhage and by "peptone" injection, was the same as before the lowering of the blood-pressure, within the limits of error of the methods used for assaying the epinephrin. A marked increase in the rate of output of epinephrin was produced by strychnin. (The above is in direct contradiction to the results of the observations reported by Cannon.—Abst.)

**A New Treatment for the Morphin Habit.**—BLUEMEL's method (*Jour. Am. Med. Assn.*, 1919, lxxii, 552) of treating the morphin habit is as follows: The patient is put to bed and his morphin stopped entirely. He is put on semisolid or liquid diet and is given cathartics as prescribed in the Towns-Lambert treatment. He thus receives three or four cathartic courses, consisting of 5 grains of blue mass with 5 compound cathartic pills at intervals of eighteen hours. Some hours after the last of these cathartic courses he is given castor oil.

In addition the patient receives from two to four intravenous infusions a day of 1000 c.c. of 0.9 per cent. sodium chloride solution. During the first few days the patient is given enough chloral at bedtime to ensure a night's sleep. Hypnotics are an important part of the treatment, as the sleep so induced blots out large periods of discomfort and fortifies the patient mentally and physically. The liquid diet is continued as long as the patient feels any nausea, and he is kept in bed during the cathartic period and until all acute discomfort from the withdrawal of morphin has disappeared. There seems to be no contra-indication to the saline treatment, and patients showed no ill effects from three or four infusions daily for a period of a week or more. The effect on arterial tension is slight and transient. Repeated infusions do not produce anemia, and the patient shows marked improvement in color. There is a decided decrease in the viscosity of the blood, which lessens capillary resistance and reduces the heart load. It was not found necessary to give cardiac stimulants to any of the patients. Six patients were treated by the foregoing method. Their average age was thirty-four years; the average period of addiction twelve years; the average daily dose of morphin was from 7 to 8 grains. The average amount of saline administered was 15,600 c.c. The stay in the sanitarium averaged fourteen days, during the first seven of which the saline was administered. Discomfort with withdrawal symptoms was not very marked, and was experienced during the first two or three days only. Most of the patients experienced considerable relief from the intravenous infusions. The stage of acute discomfort was followed by a period of nervousness and sleeplessness, which was not constant. The patient usually required hypnotics for only four nights. In two patients, who had been addicts for more than twenty years, the nervousness persisted at the end of the second week, at which time the Towns-Lambert treatment (without morphin) was given as an experiment. The nervousness diminished considerably following this second treatment. The author considers this improvement to point to some specific potency in the Towns-Lambert belladonna mixture, though the effect of the second course of cathartics and the influence of suggestion must be considered. Six other, rather milder, cases were given the Towns-Lambert treatment simultaneously with the infusions. The average age of this series was forty years; the average period of addiction was nine years; the average daily dose of morphin was  $3\frac{1}{2}$  grains. Two patients received infusions only when they manifested discomfort under the Towns-Lambert treatment; the other four received infusions from the start. The average patient was given five infusions and the infusions were not continued beyond the third or fourth day. The average patient was discharged on the seventh day. With the combination of the Towns-Lambert and the infusion treatments the patients suffered about the same discomfort as those treated by infusion alone, but they recovered more quickly from the subsequent period of nervousness. Some of them manifested a definite euphoria on the third or fourth day. Thus it would seem that the infusion treatment combined with the Towns-Lambert is better than the infusion treatment alone; however, as the two series of cases were not equivalent, the author feels that further investigation is necessary to determine the matter definitely.

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**OBSTETRICS**

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UNDER THE CHARGE OF

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**Placental Tissue as a Galactagogue.**—CORNELL (*Surg., Gynec. and Obst.*, November, 1918) has experimented with the placenta of cows prepared by washing and drying and then put up in 5-grain capsules. This dose is given four times a day for twelve doses. The first is administered as soon as the patient has recovered from labor and is able to take nourishment; it is usually given within twelve hours after delivery. A few patients objected to the odor, but aside from that there were no bad or disagreeable effects noted. The results were recorded and studied in the last 100 cases in which the preparation was given. As a comparison 70 patients entered the hospital at the same time and were placed on the same floor and were studied under the same conditions. The same food was administered to both groups of patients. The result showed that placental tissue has a favorable effect in the production of milk. Nationality and age of the patient and the sex of the child have nothing to do with the results. Among those mothers who did not receive placental tissue, 69 per cent. of the children began to gain on the fourth or fifth days, while among those mothers who received placental tissue 87 per cent. began to gain on the fourth or fifth day. Forty-four per cent. of the children regained their birth weight before leaving the hospital in cases in which the mother received placental tissue. When the mother was given no placental tissue 24 per cent. of the children had regained their birth weight before leaving the hospital. These results indicate that placental tissue has a definite value in stimulating the production of milk.

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**Thirty Cesarean Sections.**—MCLLWRAITH (*Surg., Gynec. and Obst.*, November, 1918) published a paper some ten years ago in which he described a series of twenty-seven labors occurring in women having contracted pelvis without Cesarean section. His method of treatment consisted in prophylactic version and in induction of labor. After losing three babies in close succession his method of treatment was changed. In primipara having moderately contracted pelvis the patient was given the test of labor and when this failed a section was done. Among his cases were six whom he described as obstructed labor. In these external measurements gave little or no evidence of internal contraction, but the head failed to engage before or during the first stage of labor. All the mothers made a good recovery and all the children but one, which was malformed. One of the women was thirty-six hours in labor, yet both she and her child made good recoveries. Eighteen months later she was successfully delivered of a second child by section, having declined to risk the loss of the baby by premature labor or to suffer the first stage of attempted delivery.

Another class of his cases were those in whom the pelvis was known to be contracted. Here but one child was lost, which had hydrocephalus. The mother of this child was in the medical ward of the hospital for treatment of a tubercular knee-joint. In placenta previa three cases were operated upon for this complication, mothers and children making good recoveries. The writer believes that this is the best method of treatment for those cases in which the child is viable and there is but little dilatation. In one case of accidental hemorrhage the woman was sent to the hospital after a severe bleeding. The patient was eight and a half months pregnant, bleeding very little after she entered the hospital; the fetal heart-beat was good at 120. Fifteen minutes after the examination the pulse became slow and irregular, and signs of internal hemorrhage appeared. The cervix was tightly contracted and would not admit the finger-tip. On opening the uterus a large black clot, equivalent to about a pint of blood, was found, followed by a few ounces of fluid blood. The placenta had been almost entirely separated. The mother made a good recovery, the child, which weighed  $2\frac{1}{2}$  pounds, lived a week. In the toxemia of pregnancy with convulsions the writer believes that when the cervix is not dilated and soft and treatment has failed to prevent or control the convulsion that section is the safest treatment. In cases of toxemia in which threatening signs develop before convulsions occur, prompt operation may save life, and when an anesthetic cannot be given, local anesthesia and gas and oxygen may be employed. Vaginal section is performed in a few cases: one a toxemic woman who had severe convulsions and did not long survive the operation. Another case which showed tuberculosis of the kidneys was treated by vaginal section. The third patient made a good recovery. The writer believes that this operation is well suited for cases of pernicious vomiting. In one case there was a severe chill and temperature of  $106^{\circ}$  on the fourth day. A small piece of membrane was removed and an intra-uterine douche given, after which the patient's recovery proceeded normally. Three patients were delivered a second time by section, and on examination the uterine scar was sound. As regards the history of the patients who became pregnant subsequent to Cesarean section, the writer believes that if the uterine muscle is properly sutured an infection does not occur there is but little danger of rupture. He sutures the uterine muscle with No. 2 chromic gut and over this places a continuous suture of No. 1 gut. He has as yet seen no bad results.

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**The Operative Treatment of Chorio-epithelioma.**—VINEBERG (*Surg., Gynec. and Obst.*, February, 1919), from his study of the literature of the subject and his own cases, believes there are on record between 500 and 600 cases of this condition. The writer collected in the literature 69 cases and adds 9 of his own, making a series which he studied of 78. Of these 4 were younger than twenty; 13 between twenty and twenty-five; 21 over forty, of whom 8 were fifty or over. The number of cases below twenty and over fifty years is of interest and has some relation to hydatid mole, which is most often met at the extremes of reproductive life. The condition is also found most often in those women who have rapidly conceived. The period of latency varies

from a few weeks to twenty-one years; there can be no doubt but that several years at least can elapse between the last possible gestation and the development of the condition. He quotes Ries's case as illustrating the fact that chorionic villi may remain quiescent in the body for a long time; in his patient on removing a fibroid uterus a vein containing degenerated chorionic villi was hanging from the left uterine cornu. No chorionic epithelia were found on these villi. There had been no possibility of conception for eighteen years, during which the chorionic villi had remained latent. In some cases the condition had already existed before the termination of the pregnancy. Numerous cases are quoted to prove the possibility of this occurrence. The common opinion that this growth followed hydatid mole is borne out by many reports, the percentage being estimated from 48 to 5 per cent. The most characteristic symptom of this growth is hemorrhage from the uterus, which is very profuse and may be alarming. In some cases this requires a prompt application of intra-uterine packing; in others the bleeding is moderate in amount but protracted, and resembles that caused by the retention of a piece of placenta or decidua. When bleeding returns after a curetting this circumstance should excite suspicion. When bleeding is profuse and frequent the patient becomes very anemic, and very often septic infection is added to the complication. In one of the writer's cases, the only fatal one, this occurred. The growth of the tumor usually perforates the uterus and may cause intraperitoneal hemorrhage, which resembles very closely ruptured tubal gestation. Pain is caused by the expulsion of blood-clots, and in some cases is a very annoying symptom. In the latter stages the pain is dull and the broad ligament becomes involved. Hemoptysis is an important symptom; it usually indicates that the disease is attacking one or both of the lungs. Tumors in the vaginal wall, anteriorly near the urethra, varying from an almond to a hen's egg in size, are often among the first symptoms. These tumors are deep bluish in color and appear very vascular. The uterus is usually enlarged to six or twelve weeks and the cervix is in most cases open, admitting the finger, thus giving access for exploration. Hard nodules of varying size will be felt in the uterus, with distinct excavations, or hollow in the center. If it can be distinctly proved that this condition has not been produced by curetting, a diagnosis of chorio-epithelioma can be made. In one of the writer's cases a negative report was given by the pathologist for the examination of material removed, but on exploring the uterus with the finger the writer found the characteristic condition and made a correct diagnosis. On the other hand, the uterus may be little or not at all enlarged, and in one of the writer's cases the growth was the size of a cherry, and beneath the peritoneal covering near the left cornu. In some recorded cases there were no manifestations in the genital tract, but the disease showed itself in a tumor of the brain, spinal cord or lung; thus in one case reported the patient was thought to have pulmonary tuberculosis, and chorio-epithelioma in the lung was the condition present. In another the patient developed paraplegia eight months after delivery, and at autopsy the characteristic growth was found in the spinal cord at the level of the fourth lumbar vertebra. The literature shows thirteen cases of chorio-epithelioma in the Fallopian tube, in which

the tumor varied in size from a hen's egg to an adult human head, and was very friable and bled profusely. Metastases are very frequent and take place from the blood stream; most frequent are those in the lungs at the apices or bases, then comes the vagina; the vulva is a most frequent site of metastatic growth. Occasionally a single ovarian tumor is found, but more often small nodules forming an irregular ring. They vary in consistency, size and color, but grow very rapidly, causing necrosis and lacerations. They produce profuse and obstinate bleeding, and soon become infected. The broad ligament, tubes and ovaries may also be attacked, and secondary growths are frequently found at autopsy in the liver; these vary in size and are occasionally as large as a fetal head. A tumor in the kidney may give rise to no symptoms at all, although in some cases the urine contains the characteristic cells. In the central nervous system growths are usually found at the level of the left hemisphere in the occipital lobe. There seems to be no portion of the body in which metastases may not develop. Diagnosis is often very difficult; the condition should be suspected when profuse hemorrhage follows a hydatid mole which has been thoroughly removed. Some years ago the writer urged that in these cases the uterus should be opened so that the hand may be employed to remove all vesicles; in this manner the uterus may be thoroughly examined and malignant growths detected in its very beginning. Repeated curettings are dangerous and should be avoided. In some cases amenorrhea intervenes between the removal or discharge of a hydatid mole and the first symptom of chorio-epithelioma. When growths develop soon after labor has terminated the cervix is usually open and it may be possible to palpate the interior of the uterus with the fingers. If indurated and with hard nodules, with excavations in the center, the diagnosis will be almost certain. When the growth follows an early abortion one may perform curetting and have the scraping examined by a pathologist, but the result of the examination is often misleading; only tissue obtained by very deep curetting will give a positive result on examination, and if this be done the uterus may be injured and particles of the growth may be set free to enter the circulation. The literature shows that the most rapidly fatal cases were those that had several curettings and then hysterectomy. It has been abundantly proved that curetting before operation has greatly increased the mortality. In the writer's series of nine cases there were eight recoveries, an early diagnosis having been made; while in the one patient who died two curettings had been performed. In cases in which the operator desires to avoid curetting he may follow the practice of the writer and perform vaginal hysterotomy, antverting the uterus through the anterior vaginal incision; in this way the uterus can be palpated and inspected by direct vision. As regard prognosis, if the diagnosis be made early and curettings are avoided, recovery may follow even though there have been extensive metastasis. Growths in the vagina and other portions of the body sometimes disappear spontaneously. Sometimes after the removal of the uterus small growths in the vagina disappear without further interference. Operation as early as possible gives best results, and if the patient is without any sign of recurrence six months after operation the prognosis is good, and after one year it is very much better; after two

years without recurrence, recovery may be considered absolute. The great majority of cases operated upon early recover from the operation and are free from return permanently or for a considerable time. Better results are obtained in cases following hydatid mole, because these patients are watched more closely and diagnosis made early. A considerable number of these cases follow hydatid mole, and the older the patient the more the danger of malignant growth. The writer urges that vaginal hysterotomy be done in these cases to avoid the unnecessary removal of the uterus; as soon as the diagnosis is made the entire uterus should be removed. The abdominal route, is usually the best one for this operation; there is less disturbance of the tissue and the deep pelvic veins can often be excised, which is a source of additional safety. There is no necessity for doing an operation so radical as the Wertheim operation, even though the condition seems unpromising. The presence of metastasis in other organs does not forbid operation. Radium has been tried in these cases, but with only temporary benefit. The reports of nine cases are added in detail. The reviewer in a case quoted by the writer had a patient suffering from pernicious nausea, who after the interruption of pregnancy developed symptoms of malignant growth in the brain, death ensuing, and at autopsy metastases were found in the brain, lungs, kidneys and other organs. The first unusual condition present was the pernicious nausea.

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**The Effect of Hysterectomy upon the Ovarian Function.**—RICHARDS (*Surg., Gynec. and Obst.*, February, 1919) has studied the question of the effect of hysterectomy on the ovarian function. He believes that the uterus is not essential for the continuance of ovarian function except as regards menstruation and reproduction. Those who maintain that the ovaries should be removed when the uterus is removed have not furnished convincing evidence of the correctness of their position. Ovarian function is disturbed by hysterectomy because normal menstruation is rendered impossible and during the operation injury is done to the ovary or to its circulation. The bulk of authentic evidence favors the retention of sound ovaries whenever possible.

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**The Etiology of Toxemia of Pregnancy.**—TALBOT (*Surg., Gynec. and Obst.*, February, 1919) believes that fundamental causes of toxemia of pregnancy with or without convulsions are not in the products of conception. He states the case of a woman who after incomplete abortion was curetted and developed mitral stenosis; she soon after became pregnant and had no symptoms of toxemia, but her pulse became very rapid; she was kept in bed and finally delivered by section. Four days afterward she had severe headache; seven days after the operation she had twelve convulsions and died on the following day. The pulse tension had become 180, although the bowels had moved several times daily since the operation. He also reports the case of a pregnant patient with normal blood-pressure and contracted pelvis. The urine was negative, but the patient was suffering from pain in the joints. A month later the face was slightly puffy and numbness of the greater part of the right hand appeared. There were no headache or eye symptoms. The urine was negative as regards albumin, and

but one granular cast was seen. The patient was immediately put to bed and vigorously treated with restricted diet. Albumin increased with casts and labor was brought on and a small male child born, dying twelve hours after birth. The patient recovered somewhat slowly. Six months after delivery it was found that the patient had two bad teeth near the antrum, and when these were extracted, pus was discharged. The writer in a series of 97 cases has found sepsis in the mouth arising from bad teeth in every case without exception; most of these patients had pus pockets at the root of the teeth. The writer describes a case with no evident symptoms of pus about the teeth, but roentgen-rays showed two pockets hidden in the jaw. The writer believes that the focus of chronic sepsis in some part of the body is the cause of the toxemia of pregnancy and not the fact of pregnancy. He believes that the removal of the product of conception often aids the organism to free itself from this toxemia.

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**Placenta Previa and Cesarean Section.**—BOCHEL (*Arch. d'Obst. de Gynec.*, 1918, Nos. 7 to 9) contributes a paper upon this subject, in which he describes the case of a patient, a primipara, about six months pregnant, whose pregnancy had proceeded practically normally. She had, however, been taken with fever and albuminuria, which persisted. She had an abundant hemorrhage, which was treated by tamponing the vagina. When seen in consultation the patient was pale, suffering from blood loss, the cervix long, undilated and firm. The patient was taken to the clinic, where the tampon was removed, and she became slightly better. Attacks of syncope, however, showed that pregnancy must be rapidly terminated; accordingly Cesarean section was practised and a child, about six months developed, was quickly extracted. The placenta had become partly separated but its substance was healthy, and so were the tissues of the uterus. The patient made a good recovery. She again reported when pregnant, having passed through practically a normal pregnancy, and came to the hospital in labor. She was delivered spontaneously of a living female child of normal weight. There were no complications in the third stage of labor, and the mother nursed the child successfully. In the third pregnancy the patient had a transverse position of the child, with shoulder presentation, for which version and extraction were done without injury to mother or child. Both made good recoveries. This case is cited to show that Cesarean section performed for placenta previa does not necessarily mean that the patient may have difficulty in subsequent labor. The writer discusses at some length the propriety of section for placenta previa, and concludes that in many cases major surgery is unnecessary, but that when such should be indicated, abdominal Cesarean section is the operation of choice.

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**The Transfusion of Blood for the Hemorrhages in Parturient Women.**—GUILLUM (*Arch. Mens. d'Obst. de Gynec.*, Nos. 7 to 9) contributes an extensive review of this subject. He draws attention to Dulbet's statement that women do not die because of the lack of blood cells but because of the lack of serum. On this theory is based the use of saline solution for acute anemia following hemorrhage. In order for the transfusion of blood to be successful, the blood transfused must



cause coagulation in the serum of the person who is to receive it as an evidence of the regeneration of the blood of the anemic person. One questions whether an intravenous injection of serum would not be better than a transfusion of blood. By some it is held that when the red cells have been reduced to 25 per cent. of their usual number transfusion is indicated. In choosing the method for obstetrical cases it must be simple and practical, and one which can be easily applied inside and outside of a hospital. Briau has proposed an ingenious method of the direct joining of artery to vein, which has proved successful. In hospitals cannulæ are employed with good success. Blechman has practised the direct transfusion from vein to vein. Coley, Edwards and Vaughan employ a syringe for venous transfusion. Kimpton has a glass tube by which he performs immediate transfusion. David and Curtis use a glass cylinder with cannulæ. Jeambrau uses a glass bottle whose base is drawn to a point connected by tubes, and in its circuit is a bulb cannule used for the Paquelin cautery. Foley has devised perhaps the most recent practical method for this operation; he employs a glass tube and glass bottle. It has lately been shown that two elements play an important part in restoring patients who have lost blood, one the volume of liquid, the other the number of blood cells introduced. It seems most important to dilute the blood in the serum which is used for direct transfusion. With the aid of paraffin and citrate of sodium, blood may be coagulated in the ampule of Jeambrau or Foley's tube, giving a physiological serum of 8 to 1000, which will be acceptable for transfusion.

**The Recognition and Management of Labor Injury.**—SKEEL (*Am. Jour. Obst.*, January, 1919) contributes a paper upon this in which he urges thorough examination of all parturient patients to discover injuries sustained at labor. After delivery of the placenta, gas analgesia is resumed and the patient put in the laparotomy position, the labia carefully cleansed and the anus covered by dental rubber dam or sterile towel. The cervix is inspected with a drop-light, retractors are introduced and an assistant makes pressure on the fundus and the anterior lip of the cervix is brought to the vulva; for grasping the cervix, old-fashioned sponge holders are better than tenaculum forceps. The rim of the cervix is readily examined, sometimes while the placenta is within the cervix, where it falls over the placenta as over a distended Voorhees bag. Minor lacerations are ignored. Extensive lacerations are often found without hemorrhage; they usually occur at the extreme left or right side of the rim of the cervix, extending into the base of the broad ligament; they involve the vault of the vagina. Sometimes a transverse tear or cut of the anterior lip, parallel to the rim of the cervix, is found, caused by the pinching of this part between the hand and the pubis. If the inner surfaces of the cervix be inspected, tears may be discovered produced by the rubbing action of the head as it is moved outward in delivery. Tears in the upper end of the vagina are not infrequent and are not detected by the usual method of separating the labia and looking at the perineum; they are often difficult to repair, but with the patient under an anesthetic much can be done to prevent the adhesions which often form between the cervix and vaginal tissue if such tears are not closed

by suture. The upper vagina is often torn in the performance of obstetric operations; these tears involve the midportion of the lateral vaginal wall; they are readily closed, with good results. To inspect vaginal injuries pressure on the fundus is removed, the cervix holder taken off and firm pressure is applied to the cervix, pushing the entire uterus upward, thus smoothing out and distending the relaxed vaginal vault; vaginal retractors aid greatly. There is no danger of closing the cervical canal so closely as to interfere with drainage; the extreme lower rim of the cervix is so thin that it would not unite if sutured. The last stitch is placed from one-third to one-half inch from the edge. In closing tissues high up it is often of advantage to place the lower one first, using it as a tractor to expose the upper laceration. Tears of the anterior segment are not uncommon and should be detected and repaired; this is especially true of those of the subpubic region. In repairing the pelvic floor and perineum, sutures of catgut should be employed; tears should be thoroughly brought together. The good results of closing the cervix have been seen in a small number of cases of subinvolution and retroversion. In order to prevent retrodisplacement, patients should lie early on the abdomen, and on the tenth or twelfth day begin the knee-chest posture. In 350 confinements the cervix and upper vagina have been examined in 180. Multipara with known old lacerations are not examined if infection was considered present; no such manipulation was practised. In the 180 cases the cervix needed repair in 51, and in 9 of these there was some good reason for not performing the operation. Of 43 repaired at delivery, 7 were unsuccessful, about 16 per cent.; the remainder gave excellent primary union. There was one infection in the entire series of 180; this patient was subjected to prolonged uterine manipulations, both manual and instrumental. The use of gas has been a great help in these cases to get primary union. Vaginal examinations during labor should be entirely avoided or limited as much as possible. The cervix should be immediately inspected after labor and repaired if necessary, and this procedure reduces subinvolution and uterine displacement. In lacerations of the second degree of the perineum and pelvic floor the use of upward suture of catgut permits accurate closure and restoration of the parts. Lacerations in the posterior segment of the pelvic floor are more successfully repaired than those in the anterior, hence the obstetrician should avoid pressing against the anterior vaginal vault in delivering the head.

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**Painless Childbirth and Safe Conduct of Labor.**—SCHWARTZ (*Am. Jour. Obst.*, January, 1919) gives the results of his study of 1000 cases of labor, both ward and private patients, who received the same care. The anesthetic and analgesias employed were chloroform, ether and nitrous oxide. Scopolamin, morphin and narcophin were used in a few cases and chloral hydrate was employed in a few cases of eclampsia; ethyl chlorate in only 4 cases by itself, but in a large number of cases in connection with scopolamin-narcophin treatment. These substances should only be used when the obstetrician is in constant attendance at the bedside of the patient; or it is often desirable to use several of these agents in succession. Nitrous oxide and scopolamin, he states, are comparatively harmless for mother and child; chloroform and ether

are not so harmless for the mother and distinctly dangerous for the child, while the same statement applies to morphin. These substances when used by a competent obstetrician do not tend to produce postpartum hemorrhage. He believes that pituitrin used before delivery and ergot employed after make it possible to regulate the uterine contractions during labor and prevent postpartum relaxation of the uterus. In these cases 10 per cent. receiving no anesthetic of any sort, as they did not require it, were seven children stillborn and one died soon after delivery, making 10 per cent. fetal mortality among mothers who received no anesthetic. Chloroform was used exclusively in 377 cases (or 37.7 per cent.), of whom 115 were primipara and 262 multipara. Chloroform is most dangerous to fetal life, causing profound asphyxia; 11 children were stillborn under chloroform and 9 so deeply asphyxiated as to require artificial respiration, with 17 fetal deaths, or a mortality of 4.5 per cent. Ether was given exclusively in 54 cases, mostly toxemia and eclampsia; it was used when chloroform seemed contra-indicated; it often affects the fetus. The mortality rate among the children was 16.6, but these children were born in cases already complicated by severe maternal disease. Nitrous oxide and oxygen were used in 69 cases. In 1880, at Petrograd, Klikowitsch used this anesthetic extensively and published his result in the following year; American physicians have recently used it extensively; it is especially useful for multiparous women, and is said to be without danger. With each pain the patient is requested to take from four to six deep inhalations and the gas is then shut off before the uterine contraction has reached its height. It is contra-indicated in valvular disease of the heart, high blood-pressure and very feeble individuals. Expense may be saved by machines so contrived that an anesthetic is constantly rebreathed by the patient while the carbon dioxide exhaled is removed by passing the gas through a tank filled with sodium hydrate. This saves over 50 per cent. of the expense. The fetal mortality in these cases is 6 per cent. Scopolamin-narcophin was used in 393 cases, with a fetal mortality from asphyxia of 4.6 per cent. Experiments with scopolamin, morphin, narcotics and narcophin show these drugs act directly on the muscle fibers of the bronchials in newborn children and the respiratory centers are depressed and there is bronchoconstriction. The writer has used scopolamin and narcophin and occasionally hyocin in place of scopolamin. Narcophin must be used in larger doses, about three times the dose of morphin. When using scopolamin-morphin in the usual way the writer confines it to the first stage of labor only. The initial dose of scopolamin is  $\frac{1}{100}$  grain for the average women,  $\frac{1}{200}$  for smaller women; with this is given  $\frac{1}{2}$  grain narcophin or  $\frac{1}{4}$  grain of morphin. This is deposited under the skin, where it will be slowly absorbed. A second injection is usually given forty-five minutes after the first, and when the complete dilatation is present, scopolamin is stopped. The test for the influence of scopolamin is the request that the patient touch the tip of the nose with the index finger while the eyes remain covered. Most patients do not require more than three injections and no more is given after the cervix is completely dilated. Where labor is prolonged by premature rupture of the membrane, this method seems to be useful. When the head is on the pelvic floor in primipara a small quantity of chloroform is

inhaled. Great care must be taken that patient is not overly affected. In multipara pituitrin is often given during the second stage. Where the patient shows idiosyncrasy against scopolamin, chloral hydrate in 30- to 40-grain doses is given by rectum.

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## GYNECOLOGY

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UNDER THE CHARGE OF

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**Ovarian Function after Hysterectomy.**—The purpose of a contribution to this subject by RICHARDSON (*Surg., Gynec. and Obst.*, 1919, xxviii, 146) is to present an analysis and impartial estimate of the existing evidence for and against retention of ovarian tissue after hysterectomy. Such a study seems both timely and desirable for two reasons: (1) because our knowledge of ovarian function has been substantially increased during recent years, chiefly through the intensive study of endocrinology, and (2) because there has arisen a sharp division of opinion among those most competent to decide this matter. One group is persistently advocating the routine conservation of healthy ovaries after hysterectomy, while a minority is vigorously condemning the practice as scientifically without justification. From his review of the subject Richardson concludes that the ovary is a glandular organ of complex function, our knowledge of which is at present far from complete although we do know that the uterus is not essential to a continuance of ovarian function, except as regards menstruation and reproduction. The advocates of total ablation have not furnished convincing evidence of the correctness of their contention since the disturbances of ovarian function attributed to hysterectomy are partly those associated with normal menstruation and partly those arising from damage to the ovary through operative trauma or disease. In a word, the weight of evidence furnished by anatomical, experimental and clinical investigations is overwhelmingly in favor of retention of sound ovaries both before and after the menopause age.

**Non-gestational Tubal and Ovarian Hemorrhage.**—Without careful study of ovarian and non-pregnant tubal hemorrhage, one might think that its occurrence was so rare as to be a novel or grotesque condition, but careful analysis of abdominal surgical work, including microscopic study, has demonstrated to BOVÉE (*Surg., Gynec. and Obst.*, 1919, xxviii, 117) that it is not a rare condition and he has made another contribution to this most interesting subject. Some of the causes that have been reported in connection with this condition are trauma, the ingestion of poisons of various kinds, the ingestion of oxytoxics and emmenagogues to interrupt a supposed pregnancy, especially when it did not exist, inflammatory changes and other pathological conditions including

neoplasms and maladjustment of the internal secretions at puberty. Hemorrhages from the Fallopian tube may occur from general conditions that similarly affect other tissues and venous stasis from circulatory disturbances or pressure from tumors may be reasonably included in a list of causes. In considering ovarian hemorrhage, it should be remembered that the hemorrhage may be confined within the ovary, constituting one or more hematomata or it may take place into the peritoneal cavity, producing, if abundant, an hematocele. In the former variety it may occur in the stroma, into new growths or into follicles in any state of development. If before or during follicular hemorrhage rupture of the follicle or of the wall about a stromal active hemorrhage occurs, the peritoneum may be deluged. Slight hemorrhage from the follicle is regarded as a normal incident of ovulation, but the loss of more than a slight amount of blood in this manner must be regarded as pathological. These ovarian hemorrhages nearly always occur during menstrual life. Non-gestational tubal hemorrhage probably has no diagnostic symptom or symptom-complex and the symptoms of ovarian hemorrhage are by no means distinctive. They vary from none known in cases of infancy found at autopsy to those at puberty resembling very closely dysmenorrhea of ovarian or cervical origin and even to those severe attacks that have caused death or led to emergency abdominal sections. Usually a history of sudden exertion that indirectly influenced the pelvic region has been followed by a very severe degree of pelvic pain, paroxysmal or quite continuous. Sometimes the pain is referred to the umbilicus or epigastrium, gradually limiting itself to the affected iliac fossa or lower abdominal zone, vomiting and collapse soon following. In some cases the pain has been well distributed throughout the abdomen and pelvis and general tenderness and muscular rigidity of the whole abdomen are usually present. Vagino-abdominal examination reveals great tenderness about the appendages. In but few cases, however, have correct diagnoses been made before operation or autopsy. The treatment of this condition consists of rest and the administration of anodynes in the milder cases while in the severer forms of the disease the same rules apply as are employed in treating ectopic pregnancy.

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**Removal of Intestines during Curettage.**—From time to time the literature presents the history of a case in which intestines are accidentally removed by an operator during the performance of a uterine curettage. Such cases usually occur when the patient is in the puerperal state, at which time the uterus is very soft and offers very little resistance to any instrumentation. Aside from the medicolegal standpoint of such an accident, such an occurrence always causes much speculation in regard to the amount of force that must have been expended by the operator in getting into such a difficulty. Some experimental work upon the cadaver has been done by ILL (*Am. Jour. Obst.*, 1919, lxxix, 29) in order to have a better understanding of the factors operative under these conditions. His work has demonstrated that any portion of the bowel can be pulled away by traction with a forceps through a rent in the uterus or vagina and that the point of separation will be the junction of the bowel with the mesentery, although in some subjects the separation will be extraperitoneal in large measure.

The one important point about this accident from a medicolegal standpoint that these experiments have demonstrated is that the mesentery cannot be pulled away from its origin at the spine, no matter how much traction is applied, but the point of separation will always be at the junction of the bowel with the mesentery.

**Tuboövarian Suppuration.**—It is commonly considered that the chief or only path by which pelvic pus from tuboövarian suppuration seeks to escape is through the posterior vaginal cul-de-sac or pouch of Douglas, and indeed this is its most frequent course. However, GREEN (*Boston Med. and Surg. Jour.*, 1919, clxxx, 179) states that not infrequently deep pus, either in or around the tube, may be reached surgically by this route before definite fluctuation is obtained, and in his experience the most useful early indications of the presence of pus are persistent high temperature and leukocyte count in spite of the usually successful palliative measures of ice, elevation and catharsis, increasingly acute tenderness in the mass of exudate behind the uterus, edema of the recto-vaginal wall and ballooning of the rectum. When any three of these signs are present, he believes that it is often wiser to go in search of pus and establish drainage through the posterior cul-de-sac without waiting for positive fluctuation than by such delay to allow the patient to suffer from protracted toxic absorption. If this is not done the inflammatory process may extend upward into an iliac vessel and pyelephlebitis occur, terminating in death. After the drainage of an abscess or tube, the inflammatory process generally subsides sufficiently to permit subsequent safe laparotomy, or may even recover without sufficient residua to demand further surgical intervention. Merely because tuboövarian suppuration usually points to the posterior cul-de-sac should be no reason for overlooking the other avenues by which it may escape. The pelvic abscess which accumulates in the pouch of Douglas may equally well point or be evacuated through the rectum as through the vagina. For this reason, rectal or combined examination with the fore and middle fingers should never be omitted. Other sites in which pus may point are the inguinal canals and through the linea alba, and Green cites cases of each type and urges palliation first, followed soon by drainage if unrelieved.

**Ectopic Pregnancy.**—Critical analyses and collective reviews on this most interesting subject almost always invite the attention of any physician and for this reason the recent review of the gynecological material and records at the Johns Hopkins Hospital by WYNNE (*Bull. Johns Hopkins Hosp.*, 1919, xxx, 15) is of interest. Of the 22,688 patients admitted to the service during the past twenty-seven years, there were 303 cases of extra-uterine pregnancy, an incidence of 1.3 per cent. The youngest patient was a fifteen-year-old white girl, the oldest was a forty-five-year-old negress. Sixty-one per cent. of the cases occurred in patients between twenty-four and thirty-three years of age, 7 patients were under twenty and 10 were over forty years old. The most common causes for which the patients sought medical attention were pain (84 per cent.), bleeding (31 per cent.) and tumor (7 per cent.). A history of abdominal pain was obtained from 300 patients, the other 3 patients stated positively that there had been no abdominal

pain or discomfort and each of these 3 patients presented an unruptured tubal pregnancy without any evidence of clot or free blood in the peritoneal cavity, therefore the common appearance of pain as a symptom in this condition is most probably caused by the irritation of blood in the peritoneal cavity. The onset of symptoms may be acute without other prodromal symptoms, although there is usually a history of a missed period or of irregular bleeding. In a second type there is an acute attack following prodromal symptoms, which the patient sometimes ascribes to her pregnancy. A third type of patient gives a history of gradual onset without an acute attack. Recurring attacks of pain occurred in 34 per cent. of the cases; some patients complained of soreness and tenderness rather than of definite pain. In several instances the pain was of several years' duration, generally with a recent exacerbation, but in each instance at operation some other condition, usually chronic pelvic inflammatory disease, was also present. Thirty-four per cent. of the patients stated definitely that they had missed one or more periods and 10 per cent. said that their last period had been overdue for from one to five weeks, while 17 per cent. had noticed that the last period was abnormal in some other respect. Nausea and vomiting occurred in a few cases, as in normally pregnant women and the patients with these symptoms considered themselves pregnant. In the great majority, however, there was a history pointing to intraperitoneal hemorrhage before nausea or vomiting had occurred. In no case was a positive Hegar's sign recorded, vaginal cyanosis was not marked in any case and Wynne believes that most cases of tubal pregnancy show no very definite gross changes in the cervix and uterine body, unless the fetus is living. Abdominal tenderness is frequently absent but pelvic tenderness is usually marked, especially when the pelvis is filled with recent clots. The temperature on admission to the hospital was less than 101° F. in 91 per cent. of the cases, but the majority of patients showed some increase in both pulse-rate and temperature. The correct diagnosis was made before operation in 46 per cent. of the cases, in 33 per cent. of the cases the condition was not diagnosed, while in the remainder of the cases, ectopic was either suspected or diagnosed while the patient was under anesthesia prior to being operated upon. The classical case of an acute ruptured ectopic pregnancy is usually clear if a satisfactory history can be obtained, but there are a great many cases in which the history points equally well to pelvic inflammatory disease. The latter disease also gives symptoms that not infrequently strongly suggest extra-uterine pregnancy. Concerning the method of treatment that was applied in this series, the study showed that laparotomy by the abdominal route was preferred in all cases except those in which there was a pelvic hematocoele with symptoms and signs indicating infection. In such cases, pelvic puncture and drainage is usually a safer procedure, although a secondary laparotomy may be necessary later for continued pain. The convalescence is usually more satisfactory when a careful peritoneal toilet is performed and all blood clots removed, provided that the condition of the patient warrants the expenditure of time, but irrigation of the peritoneal cavity has been discontinued. Drainage is not employed unless there is some evidence of infection in the pelvis or a general ooze following the release of adhesions. It is interesting to note that tubal rupture occurred in 61 per cent. of the

cases, tubal abortion in 19 per cent., while in 20 per cent. of the cases the gestation was unruptured. Of 96 patients in whom there was a possibility of pregnancy after the operation, 36 have since become pregnant one or more times and 61 pregnancies have resulted in 37 full-term children. In 16 cases the pregnancy ended in miscarriages and 6 patients had a second extra-uterine pregnancy.

**Tuberculosis and Cancer.**—The theory prevailing among the majority of physicians for a number of years, and still prevailing among a few, that tuberculosis and malignant neoplasia are antagonistic, has not been borne out by facts, according to BRODERS (*Jour. Am. Med. Assn.*, 1919, lxxii, 390), of the Mayo Clinic, who has devoted his attention to a consideration of this subject. He states that the fact that some tissues or organs are, to a certain degree, immune from one or the other or both of these diseases does not prove that the two diseases are antagonistic. If the observations of Naegeli are correct, in which he showed that in 93 per cent. of 420 necropsies on adults more than eighteen years of age, either active, latent or healed tuberculosis had been present, then it is reasonable to believe that similar findings should prevail in an equal number of persons who have died with malignant neoplasia. Furthermore, it would seem that the reason that pathologists are not finding tuberculosis more frequently at necropsy in persons who have died from malignant neoplasia is that the pathologists are satisfied to find the malignant neoplastic condition, and therefore fail to make a thorough search for tuberculosis. Since the surgical pathologist's examinations are limited to the tissue removed by the surgeon, he is greatly handicapped in the search for the two conditions associated, while the pathologist doing a necropsy has access to a large part or the whole of the body. The fact that active tuberculosis occurs most frequently in persons under forty-five years, and malignant neoplasia, especially epithelial tissue malignant neoplasia, most frequently in persons over forty-five, does not prohibit the association of latent and healed tuberculosis with malignant neoplasia, and, as a matter of fact, in the series of twenty cases that the writer studied the two conditions were associated in the same microscopic field seven times (35 per cent.).

## DERMATOLOGY

UNDER THE CHARGE OF

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**A Positive Wassermann Reaction in Some Tuberculous Affections of the Skin.**—SCHAUMANN (*Ann. de dermat. et de syph.*, 1918-19, No. 1) has obtained a strongly positive Wassermann reaction in two cases of tuberculide, including under this term erythematous lupus.



The first case was a woman, aged thirty-eight years, who presented two patches of erythematous lupus on the cheek, along with swollen lymphatic glands; she gave a strongly positive Wassermann reaction. Three years later she was seen again, when, in addition to the erythematous lupus, she presented ulcerating nodules on the legs, the papulonecrotic tuberculide; again the Wassermann was strongly positive. Intramuscular injections of gray oil were without effect upon the ulcerating lesions of the legs. The second case was one of papulonecrotic tuberculide, and in this case there was likewise a positive Wassermann reaction. The author was quite certain that neither of these patients was syphilitic. (It may be observed here that not all authorities are agreed as to the tuberculous character of erythematous lupus.—M. B. H.)

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**Pediculosis Pubis Due to the Head Louse.**—NICOLAS and MASSIA (*Ann. de dermatol. et de syph.*, January, 1916) have observed an example of pediculosis of the pubic region, due to the pediculus capitis. As is well-known, it is rare for the various species of pediculi to be found outside their normal habitat, although the pediculus pubis is found occasionally on the axillary hair. The authors have found but a single case similar to their own in literature. Lydston some years ago reported a case of pruritus vulvæ in a young girl which was found to be due to the pediculus capitis.

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**Dermatitis Coccidiosa.**—SEILIN (*Med. Record*, March 1, 1919) reports, from Chicago, a new case of this most interesting dermatosis. The patient was a cigar maker, aged thirty-two years. On the right palm, at the base of the thumb, was a dry scaly area, about  $2\frac{1}{2}$  inches square, which contained a number of painful fissures, with thickened edges, and about a dozen deep-seated vesicles. Scattered about this patch were a number of very small superficial abscesses. Microscopic examination of the contents of the vesicles revealed the presence of hundreds of coccidia. The affection had begun nine years before, with the appearance of a few hard papules in the palm, accompanied by intense itching. The treatment consisted of the application of a 1 per cent. solution of copper sulphate after opening the vesicles, the internal administration of potassium iodide and hypodermic injections of emetin hydrochloride. The effect of the treatment was remarkable; within twenty-four hours improvement was noted and within five days the patch was completely healed.

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**An Unusually Extensive Case of Symmetrical Keratoderma.**—VILVANDRÉ (*British Jour. Dermatol.*, October–December, 1918) reports an extraordinary case of keratoderma recently under his observation in the London Hospital. The patient was a girl, aged five years, who presented no other abnormality than the condition of the skin. According to the statement of the mother the skin was apparently normal at birth, but the affection appeared soon after. The hands, forearms, elbows, knees, lower portion of the legs and the feet presented extensive areas of greatly thickened skin, with wart-like surface and some hypertrichosis. They were grayish black in color, symmetrically situated and presented the same shape on both sides. Those on the knees were

lozenge-shaped, ending in a point some distance below the patella. The palms and soles were markedly affected and deeply fissured, presenting a bark-like appearance. There was no history of any hereditary factor. Some excellent photographs accompany the paper which illustrate the features of the case better than any verbal description.

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**Acute Lichen Planus Treated by Lumbar Puncture.**—PERNET (*British Jour. Dermatol.*, July–September, 1918) at a recent meeting of the Dermatological Section of the Royal Society of Medicine presented a case of acute lichen planus which had been treated by lumbar puncture. The patient was an ill-nourished woman, aged fifty-four years, in whom the disease had lasted two months and was accompanied by an irritation which the patient described as “dreadful.” A lumbar puncture was done and 8 c.c. of spinal fluid removed; the severe pruritus was relieved and the eruption became pale and began to undergo involution. This was the exhibitor’s third case thus treated, and in all he had obtained good results. In the discussion which followed the presentation of the case, Pringle stated that he had employed this procedure several times, always with very satisfactory results as to the relief of the itching, but in a few days it recurred and he had not considered it advisable to make a second puncture. Bunch agreed that the treatment relieved the itching, but he did not find that it benefited the eruption.

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**Multiple Benign Basal-cell Epithelioma of the Scalp.**—ADAMSON (*British Jour. Dermatol.*, July–September, 1918) reports a new case of this affection and briefly refers to some of the cases previously reported as endothelioma capitis. The patient was a man, aged sixty-one years. On the scalp were numerous, forty to fifty, small tumors varying in size from a hemp-seed to a chestnut. They were quite firm, the color of the skin, freely movable and devoid of hair; there were also a few small lesions of a similar character on the back. The tumors on the scalp had been present for twelve years, but those on the back had been noticed for thirty years. Sections made from an excised tumor showed the features characteristic of benign basal-cell epithelioma. The author agrees with Dubreuilh and Auché that the cases of multiple tumors of the scalp which have heretofore been described as endothelioma capitis are actually basal-cell epithelioma belonging to the same group as the epithelioma adenoides cysticum of Brooke. Like this affection, it shows a marked tendency to occur in two or more members of a family. According to Dubreuilh and Auché there are no authenticated cases of endothelioma capitis.

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**HYGIENE AND PUBLIC HEALTH**

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UNDER THE CHARGE OF

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**Epidemiology of Cerebrospinal Fever at the United States Naval Training Station, Great Lakes, Ill.**—SHORT (*U. S. Naval Med. Bull.*, October, 1918) states that epidemic cerebrospinal fever is a disease caused by the meningococcus, which is spread for the most part by direct contagion from patients and healthy individuals. In military organizations the meningococcus has a predilection for young recruits, but is usually inert in the absence of depressing or resistance-lowering factors. The arguments for isolating meningococcus carriers to prevent the disease are not convincing, since consistent practice on that basis has proved not only extravagant and against military efficiency, but also impracticable and non-effective. The search for meningococcus carriers and their disposition should not cause neglect of the more generally effective and easily controlled measures of hygiene, of which the following are of greatest importance: The prevention of crowding among young recruits; the allowance of ample time for their "hardening" and "seasoning;" protection from weather, overwork and fatigue, and the use of all measures that will promote the general health of the camp.

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**Winter Hibernation of Anopheles Larvæ.**—GRIFFITHS (*Public Health Reports*, November 15, 1918, No. 46, xxxiii) states that anopheles (crucians and punctipennis, at least) pass the winter in the larval stage. That is true for northern Louisiana (for crucians) during a severe winter for that section. Evidence, though less conclusive, shows that punctipennis, at least in the larval stage, withstand a severe eastern Virginia winter. Apparently pupation does not occur at low temperature, or until ordinary room temperature obtains. In selected places considerable numbers of anopheles larvæ pass the winter as such. Larvacides should be applied in the fall sufficiently late to kill the last batch of larvæ, or before season suitable for the completion of their aquatic stages in the spring.

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**Sanitation of Swimming Pools.**—SMITH and SCHOBURG (*Am. Jour. Pub. Health*, June, 1918) state that swimming pools should be so well lighted that a submerged person can always be readily seen. Economy, therefore, suggests locating the pool at the top of a building. The waste water from the pool can then be used for flushing of closets, urinals, etc., in the building. The sides of the tank should be smooth. Four sides of the pool should be available for use, with life-rails all around.

Overflow gutters are necessary, and there should be a trip basin twelve inches below the main platform. When the tank is emptied the sides should be scraped, scrubbed and flushed, then steamed, aired and dried. Wreaths of sediment on the floor should be removed and pumps on the general plan of a vacuum cleaner are recommended. Refiltration and constant agitation of the water should prevent formation of wreaths. The water selected for the pool should be the cleanest available and not that whose source is simply the most accessible. Constant refiltration makes it possible to use a given filling a greater length of time. This is an important item in cost of maintenance and will more than compensate for the initial cost of the equipment. The tendency toward installing a plant of too small capacity should be avoided. It should be possible to refilter all the water in the tank in one day (eight-hour days are in vogue). Usual frequent attention should be given to reversal of filters, washing and steaming. Dilution should be practised sufficiently to make up the loss by splashing, etc. No definite amount can be stated. This should depend on the number of bathers, frequency of refilling, etc. As a rough working rule, it is suggested that the dilution be sufficient to amount to one filling between refillings. Refillings should be determined by the number of bathers, size of pool, and bacterial content as there is no direct relationship between the number of weekly refillings and the sanitary condition of water. The general appearance of the water counts for nothing. Both calcium hypochlorite and copper sulphate have advantages, the latter probably being the favorite for chemical disinfection. Either should be used in strengths increasing from 0.5 part to 1,000,000 of water, depending on the size of the pool, number of bathers, the hardness of the water, and the bacterial reduction obtained. Bleach must be tested frequently for available chlorine. It quickly disappears from the pool. Full shower bath with soap should be demanded of all bathers. To make this possible the shower apparatus must be inspected very frequently. Instruction should be given bathers in the purpose of the bath. Especial attention should be given to the perineal region. When water strikes a person's body the natural tendency is to urinate. This should occur in the shower, not in the pool. The floor should be taken care of to prevent tracking the dirt, bacteria, etc., which have been washed off by the shower, onto the deck about the pool. On the pool platform inspection of every entrant should be performed. Bathers should wear no clothes. If this be impracticable, the authorities of the pool should furnish the suits—one-piece, undyed, scanty—and see that they are properly sterilized and dried between using.

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ORIGINAL ARTICLES

**DIGITALIS THERAPY: SATISFACTORY EFFECTS IN CARDIAC  
CASES WITH REGULAR PULSE-RATE.**

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IN general practice, very commonly the physician fails to get thoroughly satisfactory results from the use of digitalis. As cardiac patients come to the hospital very frequently we find them in a stage of markedly broken compensation though their physician has been prescribing digitalis; and yet in the hospital they respond promptly and effectively to digitalis therapy. Why is this? In part the explanation lies in the fact that under hospital *régime* the patient remains in bed and more completely rests than he is willing to do at home, even though his physician repeatedly has urged upon him the great importance of rest. This more complete rest is an important factor in the patient's improvement, but that it is not the sole factor is shown by observations that I have often made that hospital rest alone does not give the result that is obtained later when it is combined with digitalis therapy.

It seems to me that the chief factor in the failure to get good results from digitalis lies in the improper use of that drug; most commonly the dosage given is insufficient. Insufficient dosage is in part the physician's fault; in part it is due to a poor digitalis preparation furnished by the druggist.

The physician is prone to give quite small doses of digitalis and usually fails to push his dosage to the point of tolerance, as should be done unless a definite effect is produced sooner. How digitalis

should be used was tersely stated by William Withering<sup>1</sup> in 1785. "Let the medicine be continued until it either acts on the kidneys, the stomach, the pulse or the bowels; let it be stopped upon the first appearance of any one of these effects." To this might be added, "Until it acts on the respiration." Were this the rule followed to-day our practitioners would see much better results follow digitalis than they usually do.

It seems that in our books and in our teaching, bad effects from overdosage of digitalis and descriptions of contra-indications to its use have been so emphasized that often the physician actually is afraid to give an adequate dose of digitalis. In a quite extensive hospital experience with cardiac cases I cannot recall a single case admitted from the care of an outside physician in which too much digitalis had been given. Sometimes I have suspected that this was the case from an existent heart-block or from coupling of the beats, or from depression of the T-wave in the electrocardiogram or from nausea and vomiting; but in these cases usually time has shown that heart-block, coupling or depressed T-waves were due to muscle lesions, not to digitalis, and nausea and vomiting were caused by cardiac decompensation, not by digitalis; these patients really needed more digitalis. Per contra, I have seen a great number of cases sent to the hospital really because they were doing poorly on account of the fact that their physician was giving them too little digitalis.

The insufficient dosage of digitalis very frequently is due to the fact that the digitalis preparation is weak; that is, it is far below standard pharmacopeal strength. This has been well emphasized by Pratt<sup>2</sup> in some excellent studies. It seems surprising that poor digitalis is dispensed so frequently when excellent digitalis is grown in many parts of our country, and the testing of the digitalis is reasonably simple.

A great deal of nonsense, in my opinion, is written about digitalis that does not upset the stomach, and much effort appears to be used by our pharmaceutical houses to prepare such forms of digitalis. Most of them do not cause nausea, I suspect, because they are weak forms of digitalis. The fad of fat-free digitalis is an excellent example of this wasted energy. Were this effort directed toward securing a potent active leaf, without which no good digitalis preparation is possible, far better results would obtain. During the past two years I have been using at the Peter Bent Brigham Hospital excellent digitalis grown in Virginia, in Minnesota and in Washington, furnished me by friends. Now the supply of this is exhausted and the leaf furnished by Squibb this month is only half the efficiency of these other leaves, and so preparations made from it will be pro-

<sup>1</sup> An Account of the Foxglove and Some of its Medical Uses, with Practical Remarks on Dropsy and Other Diseases, Birmingham, 1785.

<sup>2</sup> Boston Med. and Surg. Jour., 1910, clxiii, 279; and Jour. Am. Med. Assn., 1918, lxxi, 618.

portionately inefficient. In passing, I should say that, in my usage of digitalis, preparation plays no part, for I have long since learned that the powdered leaf made freshly into pills is as satisfactory a form of digitalis as either tincture or infusion, and if the leaf is good, just as effective as digipuratum and digifolin, and far less expensive.

Another cause of too small dosage of digitalis lies in the common practice of prescribing tincture of digitalis by drops, and counting a drop as a minim, whereas it generally takes two or three or even more drops to make a minim, as has been emphasized by Pratt<sup>3</sup> and others. Digitalis should be prescribed in weighed or measured amount, not by drops, and enough should be given of a reliable preparation (that means a good leaf as the starting-point of the preparation) to produce a definite effect at least within four days; usually an effect is noted to begin in half this time.

Another reason for not getting good results from digitalis, I think, lies in the very general belief that myocarditis in some way is a contra-indication to digitalis or is a condition in which good therapeutic effects are not to be expected. In my experience in chronic myocarditis, a condition which is a very frequent cause of cardiac failure in people beyond forty, as I have shown in a recent study,<sup>4</sup> most excellent results follow an adequate digitalis therapeusis, and there are no contra-indications to its use, for even in those cases advanced beyond the bound of a therapeutic response no bad effects follow digitalis. In the same way there still lingers the tradition that aortic insufficiency contra-indicates digitalis, because digitalis would prolong diastole and the large regurgitant flow of blood under these conditions would stop the heart in diastolic paralysis; a good enough theory, only it seems to have no basis in fact.

Finally, and this is what I started out to emphasize, very excellent results follow digitalis in hearts that are not fibrillating. Mackenzie, in particular, has so emphasized the value of digitalis in auricular fibrillation that many seem to think if the pulse is regular, digitalis is not liable to give good results, and so it is not pushed in cases with regular rhythm. Pratt<sup>5</sup> says: "My experience with this method has demonstrated that large doses are not dangerous when the cases are carefully followed, and that the drug gives brilliant results in heart failure associated with auricular fibrillation, as Mackenzie has shown, and that it is beneficial in some cases of heart failure with normal rhythm. In hearts with normal rhythm, slowing of the pulse is still generally regarded as a measure of digitalis action, but my observations confirm the findings of Mackenzie<sup>6</sup> and Cohn and Fraser<sup>7</sup> that the drug rarely slows the pulse except in auricular

<sup>3</sup> Jour. Am. Med. Assn., 1918, lxxi, 618.

<sup>4</sup> Christian: Jour. Am. Med. Assn., 1918, lxx, 1909.

<sup>5</sup> Ibid., 1918, lxxi, 618.

<sup>6</sup> Heart, 1911, xi, 273.

<sup>7</sup> Tr. XVII International Congress of Medicine, Sec. VI, Medicine, London, 1914.

fibrillation until toxic symptoms are produced. . . . It rarely seems to be of benefit in myocardial weakness due to aortic insufficiency, but this valvular lesion is not a contra-indication of its use, as was taught by Corrigan. . . . Rowland, working under Mackenzie, concluded, according to a statement made in the text-book of the latter, that in cases of heart disease with regular rhythm, strophanthin intravenously had very little effect on the general condition and no effect on the pulse-rate or blood-pressure."

Of course, it is in the cases with auricular fibrillation that the brilliant results of digitalis are seen most commonly, but I have seen frequently just as good results in chronic cardiac cases with edema in whom there was no irregularity of the pulse or only an occasional extrasystole. The following cases illustrate this very well.

CASE I.—P. B. B. H., Med. No. 4963, a man, aged fifty-nine years, was admitted to the hospital on July 10, 1916. Fifteen months before he began to have dyspnea on exertion, and this progressively increased. For thirteen months he had had swollen legs. For twelve months there had been nocturnal dyspnea, severe enough for three months to compel him to sleep sitting in a chair. On admission he had dyspnea, marked subcutaneous edema and ascites. His heart was markedly enlarged, regular in rhythm, and a soft systolic murmur was audible over the precordium. His blood-pressure was: systolic, 220; diastolic, 170. He was considered to be a case of chronic myocarditis and hypertension. At 6 P.M. on July 10 he received 0.1 gm. of powdered digitalis leaves, and this was repeated three times a day until 6 P.M. on July 13, a total of ten doses, or 1 gm. The next day he was begun on 0.05 gm. of powdered digitalis leaves twice a day, and this was continued during his stay in the hospital. The effect of the digitalis therapy is seen in Chart I, where it will be seen that the pulse was not slowed, it being already slow (82), but a striking diuresis and loss of weight occurred (18 kilos, or 39.6 pounds in four days); in the language of Withering, an action on the kidneys.

March 26, 1917, this patient was admitted again with a quite similar condition. Electrocardiograms taken at this time showed left-sided muscular preponderance and a rare auricular extrasystole. From 10 A.M. on March 26 to 12 noon on March 29 he received 0.1 gm. of powdered digitalis leaves four times a day, a total of fourteen doses, or 1.4 gm., and from 6 P.M. on March 29 to 10 P.M. on March 31 a similar dosage twice a day, or a total of 1.8 gm. of digitalis leaves in five days. The result (Chart II) as before was a striking one, with diuresis and a loss in weight of 29.4 kilos, or 64.6 pounds in thirteen days.

June 14, 1917, he was admitted for the third time with a similar prompt diuresis following digitalis, and a loss of weight, 18.8 kilos, or 41.3 pounds in ten days.

September 25, 1917, he came in for the fourth time. A larger amount of digitalis and a longer time were required to produce a



diuresis. On September 25 he received digitalis leaves, 0.1 gm. every two hours for five doses. No digitalis was given on September 26 and 27. On September 28 he received four doses of 0.1 gm. at two-hour intervals and then the same does four times a day until 2 P.M. September 30, a total of 1.9 gm. of digitalis since admission. On September 30 diuresis began as shown in Chart III and continued until October 21. From October 1 to 16 he received 0.1 gm.

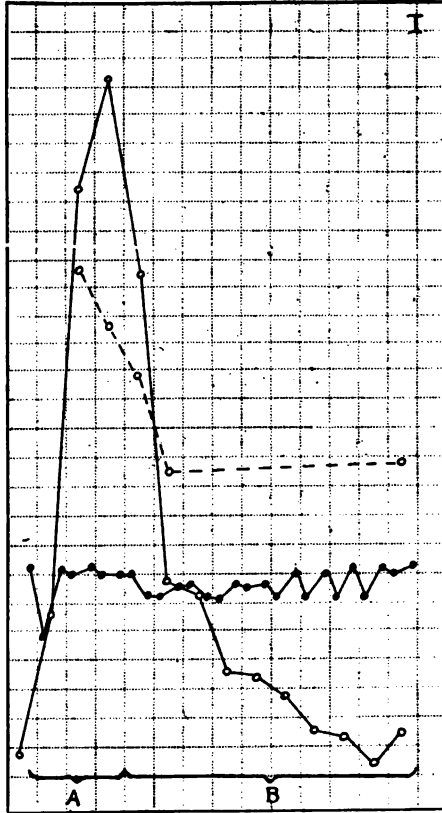


CHART I.—Solid line connecting dots indicates pulse-rate; solid line connecting circles, twenty-four-hour amount of urine in cubic centimeters; broken line connecting circles, weight in kilos; "A," powdered digitalis leaves 0.1 gm. three times a day; "B," powdered digitalis leaves 0.05 gm. twice a day.

digitalis leaves three times a day: in all, forty-six doses, or 6.5 gm. from admission to its discontinuance. During this period his weight decreased 20.2 kilos, or 44.4 pounds. Electrocardiogram at this time showed no arrhythmia.

His fifth admission was on December 3, 1917. Now digitalis produced relatively little effect. By December 26 his auricles had gone into fibrillation, and this persisted. He steadily grew worse

and died April 3, 1918. Autopsy showed chronic myocarditis without valve lesion.

In a similar case, that is, one with chronic myocarditis (P. B. B.H., Med. No. 155) admitted June 24, 1913, the effect of strophanthin given intravenously was quite evident, especially on the pulse-rate as

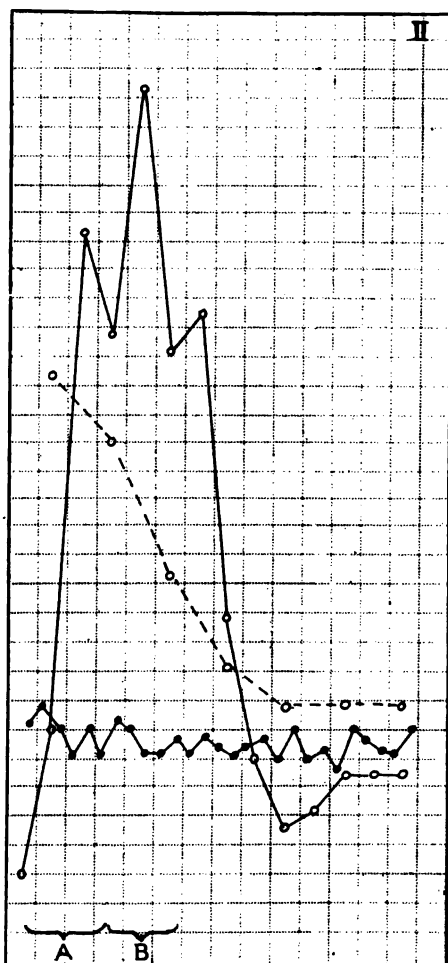


CHART II.—Solid line connecting dots indicates pulse-rate; solid line connecting circles, twenty-four-hour amount of urine in cubic centimeters; broken line connecting circles, weight in kilos; "A," powdered digitalis leaves 0.1 gm. four times a day; "B," powdered digitalis leaves 0.1 gm. twice a day.

shown in Chart IV. One c.c. containing 1 mgm. of strophanthin was given intravenously at 5.10 P.M. on June 25, 3.45 P.M. on July 3 and 11.30 A.M. July 7. The pulse slowed from an average of 120 to 75. This patient had a regular pulse. Diuresis was not so marked in this patient as in the preceding, but he did not have such marked edema.

His general condition was strikingly improved by the therapeusis. This case is cited, owing to the statement of Rowland, from Pratt's paper. In this case strophanthin intravenously had a

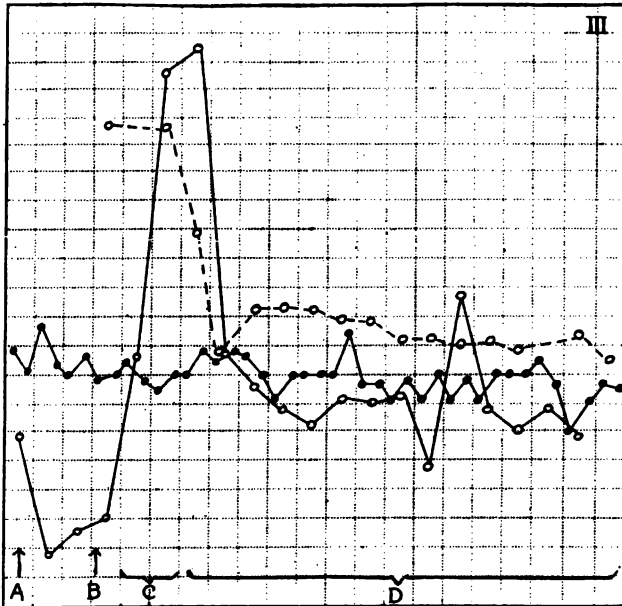


CHART III.—Solid line connecting dots indicates pulse-rate; solid line connecting circles, twenty-four-hour amount of urine in cubic centimeters; broken line connecting circles, weight in kilos; "A," powdered digitalis leaves 0.1 gm. every two hours for five doses; "B," powdered digitalis leaves 0.1 gm. every two hours for four doses; "C," powdered digitalis 0.1 gm. four times a day; "D," powdered digitalis leaves 0.1 gm. three times a day.

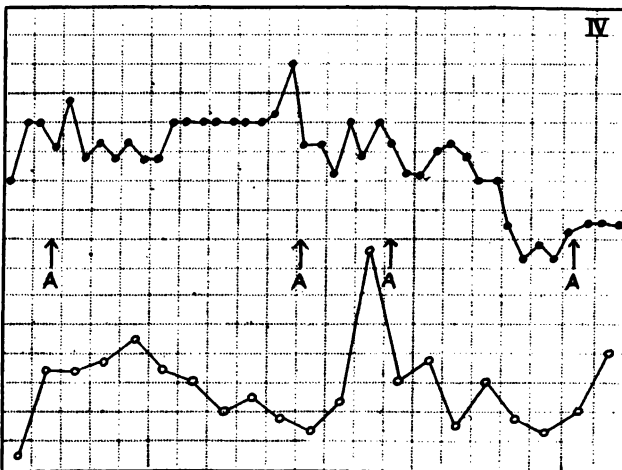


CHART IV.—Solid line connecting dots indicates pulse-rate; solid line connecting circles, twenty-four-hour amount of urine in cubic centimeters; "A," 1 c.c. containing 1 mgm. of amorphous strophanthin intravenously.

very satisfactory effect on both pulse-rate and general condition. The dosage of amorphous strophanthin (Böhringer) used was larger than I would at present advise. A 0.5 mgm. repeated once again in the twenty-four hours is safer than a single dose of 1 mgm.

CASE II.—Another case (P. B. B. H., Med. No. 2767) shows a good result from digitalis in slowing the pulse-rate (Chart V). This was a man, aged thirty-five years, admitted several times to the hospital. On this admission, May 10, 1915, he was very dyspneic, with Cheyne-Stokes respiration, his heart was enlarged, with a loud blowing systolic murmur heard all over the precordium. His liver was enlarged and pulsating. He had no ascites, no hydrothorax and but little subcutaneous edema. His pulse was alternating but regular in rhythm and electrocardiogram showed only the complex of left-sided muscle preponderance. His condition was considered

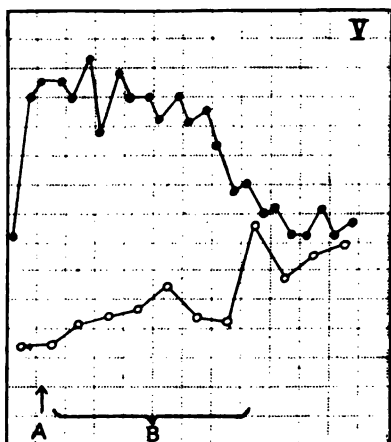


CHART V.—Solid line connecting dots indicates pulse-rate; solid line connecting circles, twenty-four-hour amount of urine in cubic centimeters; "A," 1 c.c. of digipuratum intramuscularly; "B," powdered digitalis leaves 0.1 gm. three times a day.

to be chronic myocarditis. On May 11 he received 1 c.c. of digipuratum intramuscularly and was started on powdered digitalis leaves three times a day. This was continued to May 18, a total of twenty doses, or 2 gm. of the powdered leaf. Besides other changes the pulsus alternans entirely disappeared.

One more case may be cited.

CASE III.—A man, aged thirty-five years (P. B. B. H., Med. No. 6293), was admitted on March 16, 1917, complaining of shortness of breath and swelling of the legs. He had edema, ascites, moderate hydrothorax and a markedly enlarged heart without murmur. He had a pulsus alternans, and electrocardiogram showed distorted ventricular complexes, but no irregularity of rhythm. On the fourth day in the hospital, March 19, he was started on digitalis leaves, 0.1 gm. four times a day, and this was continued until

March 24, a total of nineteen doses, or 1.9 gm. of digitalis leaves. The pulse was moderately decreased in rhythm (Chart VI), a diuresis was produced and his weight decreased in six days 10 kilos or 22 pounds. This patient came again to the hospital on April 6, 1917, for recurrence of his symptoms. On April 6, in the evening, he received 0.2 gm. digitalis leaves and next morning began to receive 0.1 gm. of the same three times a day. This was continued until April 12, or sixteen doses, a total of 1.8 gm. of digitalis leaves, including the first dose of 0.2 gm. This slowed his pulse and produced a diuresis as shown in Chart VII. At each time the patient's

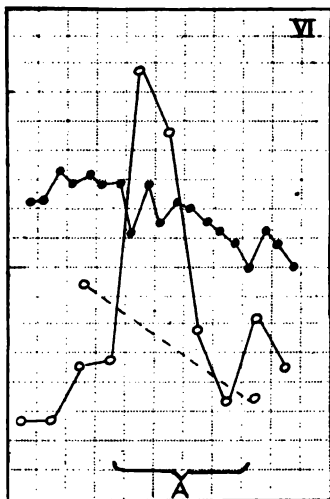


CHART VI.—Solid line connecting dots indicates pulse-rate; solid line connecting circles, twenty-four-hour amount of urine in cubic centimeters; broken line connecting circles, weight in kilos; "A," powdered digitalis leaves 0.1 gm. four times a day.

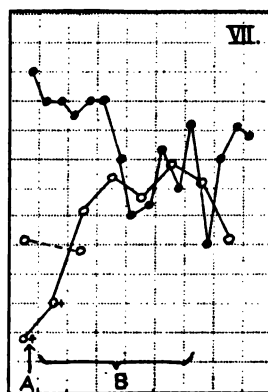


CHART VII.—Solid line connecting dots indicates pulse-rate; solid line connecting circles, twenty-four-hour amount of urine in cubic centimeters; broken line connecting circles weight in kilos; "A," powdered digitalis leaves 0.2 gm.; "B," powdered digitalis leaves 0.1 gm.; three times a day.

general condition was much improved. On a later admission this patient died and autopsy showed an enlarged heart without organic valve lesion, a case of chronic myocarditis.

In all of these cases there was a striking improvement in the patient's general condition and often a great decrease in dyspnea. The latter frequently is a very striking effect of digitalis in hearts that are regular as well as those that are irregular in rhythm. Such effects, however, cannot be presented graphically.

These cases may serve as examples of what we commonly observe in cardiac cases without arrhythmia, and justify placing much confidence in the effects of digitalis on cardiac patients with regular

pulses. They certainly justify a confident use of digitalis in such cases even though the pulse-rate may not be rapid. Even when the pulse-rate is not changed, other striking changes are produced, and the patient is benefited by digitalis therapy when it is properly administered.

## A MESOTHELIOMA OF BOTH SUPRARENAL BODIES AND BOTH LUNGS, WITH HEMOTHORAX.

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THE uncertain derivation of certain tumors of the upper pole of the kidney and its adnexum, the adrenal, has caused many neoplasms which arise in these organs to be erroneously classed as hypernephromata. Omitting those tumors described by Grawitz<sup>1</sup> as classical of the type hypernephroma, there remain many other distinct varieties of growths to which miscellaneous descriptive names have been applied. Unfortunately, many of these tumors, because of their occurrence in or about the hypernephric region, have been recorded as hypernephromata. Many have received so little description that their identity is lost, and no doubt many of special interest have not been described.

In the present consideration the occurrence of tumors in both adrenals and both lungs, identical in their histopathology and interesting in their cytological picture, together with the interesting clinical picture, form the basis of this report.

A colored male, aged forty-eight years, was brought into the Charity Hospital. He was in a moribund condition and died the following day. There is nothing pertinent in his family history. About five weeks previous to his entrance he noticed "a swelling in the right side of the chest." He had a cough and fever and suffered from shortness of breath. He suffered extreme pain in both sides of the chest, difficulty in breathing and diarrhea.

Physical examination shows an emaciated, anemic negro male, restless, anxious and dyspneic. The respirations are rapid and shallow and chiefly abdominal in type. The right side, while more prominent, is almost stationary during respiration. The supra-clavicular regions and Mohreneheim's fossæ are abnormally sunken. The right side from the third rib down anteriorly and laterally, and also posteriorly, shows a marked distention, with bulging of the intercostal spaces. No voice fremitus is felt over the entire right lung, but there is a slight increase on the left side. There is a

<sup>1</sup> Die sogenannten Lipoma der Niere, Arch. f. path. Anat., etc., Berlin, 1883, xciii, 39.

localized edema of the right chest wall. The lower edge of the liver is displaced down as far as the umbilicus. Percussion elicits flatness over the entire right chest; the left side is practically normal. Over the right lung the voice and respiratory sounds are only barely audible; over the left lung, scattered rales of the coarse and fine moist varieties are heard throughout.

The right pleural cavity was aspirated and blood withdrawn.

Upon entering the ward the following morning the patient was in a state of collapse; his pulse was very rapid and barely perceptible and he was bathed in a cold perspiration. He died shortly afterward. The clinical diagnosis made was bilateral pulmonary tuberculosis, with right hemothorax.

**AUTOPSY PROTOCOL.** Autopsy held one hour after death. Body is that of a colored male, much emaciated. Sclera yellow and pupils dilated and equal. The tissues over the chest are edematous. There are no enlarged peripheral lymph nodes. On the right side along the axilla down to the iliac crest the skin is blistered. The thyroid gland is apparently normal. The right pleural cavity is found filled with a dark brown fluid which is probably partly hemolyzed blood. At the lower portion of the cavity, clots are found. The lungs are totally adherent laterally to the costal pleura as far back as the spinal column. The right pleura is found studded with small nodular areas which give the appearance of dark skin and appear tuberculous in character. There are a number of tags on the parietal pleura, corresponding to areas where the lung was found adherent. The left pleural cavity is dry. The lung is slightly adherent to the costal pleura; it is of a gray color and is studded on the surface with small grayish nodules; it crepitates fairly well on palpation, but is very nodular. On section the organ is of a red color and presents throughout small yellowish-white and grayish-white masses, and larger areas which are necrotic in the center. These vary in size from 2 mm. to 2 or 3 cm. Some are round and others irregular in shape. The right lung presents a similar aspect, but the nodules are more numerous and in certain areas coalesce.

On opening the parietal pericardium it is found to be adherent on the surface of the heart by recent adhesions, which are easily broken up. The surface of the pericardium internally and the surface of the epicardium are studded with small grayish nodules, which are rough and nodular on palpation. The heart is otherwise negative. The spleen is totally adherent to the liver and adjoining organs. It is normal in size and of a slate color; it is firm and its capsule is very much thickened. On section it is of a red color, and the connective-tissue element is slightly increased.

The liver is found pushed down as far as the umbilicus from the fluid in the right chest. The gall-bladder is one-fourth full of a yellow fluid; the duct is patulous and free from calculi. The liver on section is of a yellowish-brown color; lobulations are not marked; nothing else of note is present.

The pancreas presents nothing apparently abnormal. The mesenteric glands are slightly enlarged. The suprarenal gland on the left side measures 3 x 6 cm. An oblong body, more or less caseous, is found herein which appears tuberculous. Kidney measures 10 x 6 cm. The surface of the organ is studded with small yellowish areas or bodies at the upper pole, contiguous with the suprarenal. The capsule is slightly adherent. The surface of the organ is granular and of a red color. Cortical substance measures 8 mm. The differentiation between the cortex and the pyramids is poorly shown. The right suprarenal measures 3 x 4.5 cm. It presents on section a yellowish mass, which fills up the whole section of the organ and measures 1 cm. in diameter. The right kidney measures 11 x 6.5 cm. On section it is of a red color. The cortical substance measures 1 cm. and presents the same general appearance as the left kidney.

The gastro-intestinal tract and pelvic and genital organs are normal. The body was claimed and the procedures were limited.

The diagnosis at first was that of pulmonary and pleural tuberculosis, pleural hemorrhage and tuberculosis of the adrenals. A more careful examination of the sectioned lung surface showed the apparent tubercles to be at the same level with the surface or even umbilicated. This point, together with their marked irregularity in shape and size, suggested a neoplasm with more or less miliary arrangement.

**MICROSCOPIC EXAMINATION.** Sections were stained by eosin-hemotoxylin, phosphotungstic hemotoxylin and Mallory's stain for connective tissue.

*Suprarenal Glands.* The tumors of both suprarenals being identical in their picture are described as one. Transverse sections of the adrenal and tumor show the neoplasm separated in part from the gland by a connective-tissue capsule, but farther on this discontinues or is reflected at an acute angle from the gland to the tumor. Here the tumor cells merge directly into those of the gland, extending through the zona glomerulosa into the zona fasciculata, and in certain areas a few tumor cells invade through the zona reticularis into the medullary portion. In this area the growth extends directly to the bloodvessels, and although no embolic tumor cells are seen in the vessel lumina, metastasis *via* this route is suggested. The tumor in its greater extent seems to blend gradually into the fascicular zone, there being no abrupt differentiation of tumor and normal structural cells. In the proximal portion of the tumor the cells have gradually assumed an arrangement and character like those of the adrenal, but in the central and distal or peripheral portions the intercellular reticulum, shown best by Mallory's stain, has massed into thick bands of stroma and the cells vary to an extreme, as compared with those of the gland, in size, shape, nuclei and staining properties, and even *inter se* in all these respects excepting the stain. The stroma as it spreads through the tumor forms in the most part alveoli, varying greatly in size and



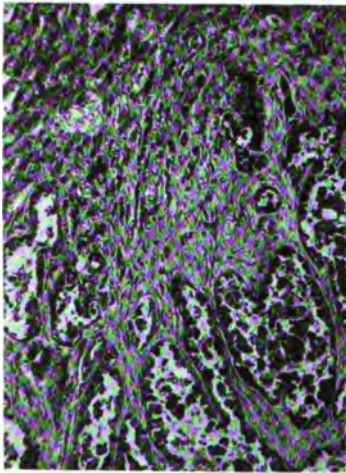


FIG. 1

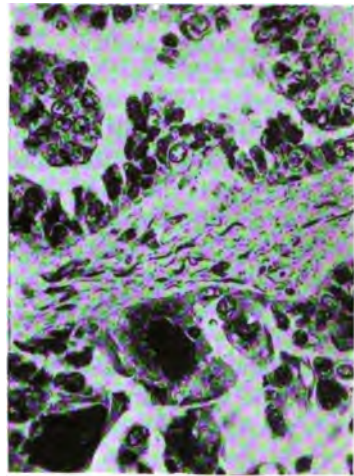


FIG. 2

FIG. 1.—Tumor of adrenal (low power). Shows the very irregular arrangement of stroma into alveolar and papillary forms. Zona fasciculata is seen in left upper quadrant.

FIG. 2.—Tumor of adrenal (high power). Shows marked irregularity of size and shape of cells. Contained within some of the giant cells are the so-called endogenous cells.

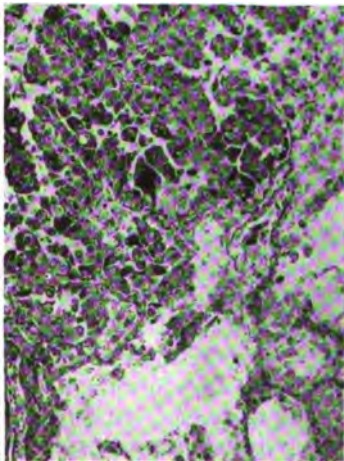


FIG. 3

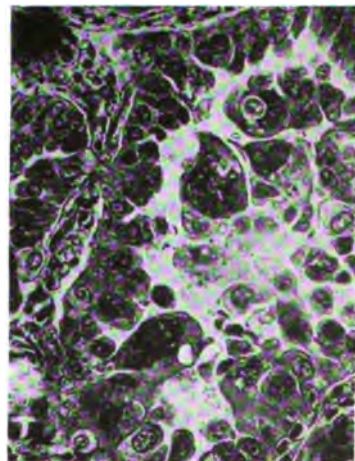


FIG. 4

FIG. 3.—Tumor of lung (low power). One of the smaller tumor foci showing alveoli filled with tumor cells; in certain areas the tumor has entirely replaced lung structure. Many of the irregular shaped giant cells are seen.

FIG. 4.—Tumor of lung (high power). Part of an alveolus showing the walls forming in part the tumor stroma. Cells of this particular area are more regular. Giant cells with cell inclusions and evidences of mitosis are seen.

shape. It also presents in part irregular projections or broad processes suggesting papillæ. These are covered with a single layer or several layers of cells. In some alveoli one or more cellular layers are seen, causing an adenomatous appearance, while others are completely filled with cells. A few small bloodvessels are seen coursing through the stroma. More interesting than the bizarre arrangement of the stroma is the study of the cells themselves. They vary to an extreme in size, shape and character of nuclei; they range from  $7\mu$  to  $30\mu$ , the larger cells being in preponderance in some fields, the smaller ones in others. In some alveoli this discrepancy in size is striking because of the juxtaposition of the giant cells with the small ones. Their shape is very pleomorphic; some are quite round, others cuboidal and others polyhedral. The nuclei bear no direct proportion to the amount of protoplasm, as some of the small cells contain very large nuclei and some of the larger cells small nuclei; as a whole, however, the nuclei of the large cells are extremely large and very coarse and present a marked reticulated chromatin network. The nuclei stain so intensely by the hemotoxylin that an apparent *bas-relief* or embossed appearance is given to them. Some of the large cells, instead of having a single large nucleus, are multinucleated, presenting from five to ten small nuclei. The nuclei are for the most part rounded, but some are very irregular, even jagged, others are almost square in shape. Numerous rosettes and other mitotic figures are present. The protoplasm stains quite uniformly a lavender color and is smooth, except for a few very minute granules. Some of the larger cells show phagocytic powers, having contained in their cytoplasm, cells appearing as lymphoid and polymorphonuclear types and still others larger and resembling some of the smaller tumor cells, the so-called "endogenous or daughter cells."

*Lungs.* Sections of the tumor from both lungs show numerous metastatic areas varying greatly in size. In some sections two or more nodules can be seen in the low power field, while in others the entire section is tumor structure. The arrangement, particularly in the small foci, is more definitely adenomatous than that of the adrenal; in the larger, however, the appearance is identical with that of the adrenal tumor, so that one could not differentiate them unless the normal histology is examined. In the small areas the alveolar walls with their coursing capillaries are seen forming a distinct network with the cell rows or masses contained within, but in the large nodules the lung structure is lost, being completely replaced by tumor elements. Necrosis is present in the large tumor foci. The bronchi are seen here and there throughout the tumor, but do not seem involved except for the fusing of the adventitia with the tumor stroma. Where the neoplasm has approached the pleura in certain areas this membrane is involved and necrosis is here and there present, accounting for the hemothorax.

The cytological features are the same as those of the tumor in the

adrenal, even to the extent of showing the interesting cell inclusions in certain of the large cells.

Microscopic study of the other tissues showed nothing of interest, with the exception of the pericardium, which showed distinct tuberculosis. Definite miliary tubercles, with central caseation, epithelioid proliferation and lymphoid and giant cells, were beautifully distributed throughout, especially the epicardium.

**SUMMARY.** The tumors of the kidney and adrenals have caused, perhaps, more discussion and diverse opinion as to their classification and origin than those of any other organ. After the embryological basis of these structures was, in greater part, agreed upon the determination of the exact derivation of the neoplasm springing therefrom has undergone and continues to undergo a very divided viewpoint. Even the recognized tumor of the Grawitz type bears very contradictory opinions as to its origin, among which are those of Grawitz,<sup>2</sup> Stoerck,<sup>3</sup> Sudeck,<sup>4</sup> Greer and Wells<sup>5</sup> and Wilson.<sup>6</sup>

In a *résumé* of the histopathology of the tumor herein described it is interesting to note the identity of the structure in both adrenals and in both lungs. This is so true that microscopic fields of tumor alone from these organs cannot be differentiated. The marked irregularity in size, shape and arrangement of the cells is striking. While the spontaneous occurrence of the same tumor type in both adrenals is not unprecedented, a metastasis to both lungs, so far as it can be ascertained, is unique. It would seem that both organs were submitted to a common etiological factor with a pathological response of uniform character. Wooley and Adami<sup>7</sup> have described tumors appearing in both adrenals somewhat similar to this tumor. The pulmonary and cerebral metastases in their case, however, were of a distinct sarcomatous type. They suggest, as regards the presence of bilateral adrenal tumor, that "the fact that the original tumors are bilateral indicates very plainly that the growth originated not in one cell or group of cells which by their growth produced a tumor, but rather in the cells of the glands, which, influenced by some biological change, lost their characteristics and retained simply their embryonic or formative characteristics." The true embryonal connective-tissue origin of such tumors is well illustrated in the metastases of their tumor by the reversion to tumors of definitely sarcomatous histology. They have applied the term "carcinoma-

<sup>2</sup> Loc. cit.

<sup>3</sup> Zur Histogenese der Grawitz'schen Nierengeschwulste, Beitr. z. path. Anat. u. s. allg. Path., Jena, 1908, xliii, 393.

<sup>4</sup> Zur Lehre von den aberrirten Nebennierengeschwulsten in der Niere, Arch. f. path. Anat., etc., Berlin, 1894, cxxxvi, 293.

<sup>5</sup> The Absence of Adrenalin in Malignant Renal Hypernephromas, Arch. of Int. Med., 1909, iv, 291.

<sup>6</sup> A Comparative Study of the Histology of the So-called Hypernephromata and the Embryology of the Nephridial and Adrenal Tissue, Jour. Med. Research, 1911, No. 1, xxiv, 73.

<sup>7</sup> A Primary Carcinomatoid Tumor (Mesothelioma) of the Adrenals, with Sarcomatous Metastases, Tr. Assn. Am. Phys., 1902, xvii, 527.

toid," which seems quite applicable, as it at once indicates its appearance, and again, that it is of other than epithelial origin.

In this instance the term mesothelioma has been employed, thinking, as suggested by Adami, to avoid confusion with Grawitzian hypernephromata, and again as indicating its probable histogenesis.

### **EPIDEMIC OF TYPHOID FEVER AT HOT SPRINGS, N. C., PRISON BARRACKS:**

CLINICAL REPORT OF 186 CASES TREATED AT THE UNITED STATES  
ARMY GENERAL HOSPITAL, NO. 12, BILTMORE, N. C.<sup>1</sup>

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THE present infrequency of so large a number of typhoid patients is sufficient excuse for a report of the epidemic.

On August 13 and 14, 1918, 152 German alien enemies were received from the war prison barracks at Hot Springs, N. C. On September 3, 31 additional cases were transferred to this hospital. An enlisted private from Hot Springs, one ward aide and one laboratory assistant from General Hospital No. 12 were included in our series.

Inadequate facilities for the care of the sick at Hot Springs was the occasion for the transfer of the patients to this hospital. The prisoners were conveyed in cots to and from baggage cars.

Every stage from the first few days to the fourth week of illness was represented. The transfer was made on two of the most torrid days of the summer. As they arrived at the hospital they were classified and accommodated in four hospital wings, with reference to the severity of the disease.

The space selected for the typhoid patients consisted almost entirely of wards with two beds, a bath connecting each two rooms.

At the end of each wing, averaging forty-six beds, a central toilet room was employed to receive the excreta. Commodes, urinals and bed-pans were used and cared for in these general toilets.

The excreta were emptied into a large volume of 2 per cent. liquor cresolis compound. The absence of any apparatus for boiling pans and urinals compelled the use of brushes soaked in cresol for cleansing purposes.

Commodities when filled were labelled with the time of last use and were emptied, after two hours' treatment, directly into the toilets.

<sup>1</sup> Assisting as Ward Surgeons in the care of these patients were: Capt. Henry L. Wenner, Lieut. Edwin Henes, Jr., Lieut. Theodore M. Sanders, Lieut. Alfred Orth.

Notwithstanding the fact that large signs "Verboten f. Patienten (Patients Must Not Use)" were placed on each toilet in the private bath-rooms, one patient used a toilet within an hour after his arrival at the hospital.

Steps were immediately taken to close with heavy wire each toilet except that in the central room. The toilets in private bath rooms remained wired until every patient in that wing had ceased to be a menace, as shown by three negative cultures of stool and urine.

During convalescence, while the patients were ambulatory, excreta were passed directly into cresol commodes in designated bath rooms, and after the usual length of time these commodes were emptied into the general toilet.

The most difficult problem to confront the administration of the service was the disposition of the linens.

The gauze reclamation room was the only available place for direct sterilization. Even though this important branch of the surgical service had been discontinued the facilities thus offered would have been quite inadequate. The above situation will be more fully appreciated by the statement that during the first two weeks an average of 942 pieces of linen were disinfected each day.

Decision was finally reached to use hot water in the bath tubs for the purpose of sterilization. Wooden covers were secured for several tubs in each wing, and soiled sheets, gowns and other linens were deposited in these tubs.

Selection of periods during the day and night when the least burden was placed upon the hot-water supply enabled us to secure an initial temperature of 78° to 80° C. After one hour, when the linens were removed, the temperature had dropped to approximately 55° C.

This arrangement was accomplished only at the expense of constant supervision, with repeated tests of temperature during the sterilization.

After one hour's treatment the linens were wrung out and conveyed in portable bath tubs to hastily improvised wires strung on poles adjoining the hospital buildings. The linens were then allowed to dry in the direct sunlight. Our skepticism of the method employed was dissipated when repeated cultures of the drippings from linens in tubs remained sterile.

The absence of large wards increased the difficulties of management, as the personnel was quite inadequate to observe delirious patients quartered in rooms accommodating two patients. One patient arose and attempted to walk, falling on the floor with a fracture of the nasal cartilages.

The success of the above method may be shown by the fact that only two cases of typhoid fever developed in the personnel of the hospital.

A careless ward aide, who boasted his immunity on account of three vaccinations within three months, contracted the disease. He persisted in carelessness, even after repeated reprimands, during the handling of bed-pans, etc.

His infection was rather severe and recovery resulted after several intestinal hemorrhages and a turbulent four weeks' illness.

A patient convalescent from empyema was employed in the laboratory to wash Petri dishes.

He apparently contracted influenza, and finally his blood culture was twice positive for *Bacillus typhosus*.

Observation of the patients as they arrived convinced us that we had to deal with a severe type of infection. A very large number were found acutely ill, many of them delirious.

Individual examination showed 70 per cent. with a generous crop of roseola typhosa. It was never a problem to determine from a few isolated spots whether they were actually rose spots. Upon the chests and abdomens of the majority a 25-cent coin could not be placed without covering a portion of the eruption. After forty-eight hours this phenomenon had subsided to a large extent, leaving us with the conviction that the intensity of the heat during their journey contributed to this luxuriant eruption.

The compilation of cases in three tables attempts to present the salient features in each case.

Table I includes deaths with their complications and the most probable cause of exitus. Unfortunately, no necropsies were permitted, which detracted from the value of our conclusions.

The laboratory service was not prepared for the large task involved in the examination of 152 patients admitted on two successive days, which accounts for the absence of data on blood cultures in many instances.

Four patients died within four days of their admission to this hospital.

Four of the fifteen deaths were caused by perforation. Of this number three were operated.

Perforation was diagnosed in the unoperated case (Case 13), simultaneously with that of Case 5. When operation in Case 5 was completed, peritonitis was evident in the other patient, who was then moribund. This latter patient had presented an extremely toxic condition, and operation was then deemed useless. Death ensued within a few hours.

In this group, parotitis had developed in 2 cases prior to admission, and their condition was grave from the first.

Lumbar puncture was repeatedly performed in the case with a complicating meningitis, but, as was to be expected from the presence of streptococci in the spinal fluid, this patient proceeded to a rapid exitus.

TABLE I.

Case No.	Age.	Date of onset.	Blood culture.	Date of admission to G. H. 12.	Typhoid vaccine.	Date of death.	Estimated day of disease at death.	Complications.	Cause of death.
1	35	Aug. 6	None	Aug. 13	Unknown	Aug. 17	11th day of disease	Perforation of ileum August 16	Shock from operation.
2	30	July 24	Positive 16th day of disease	Aug. 14	Unknown	Sept. 8	46th day of disease	1, decubitus; 2, streptococcus meningitis; 3, edema of lungs	Meningitis; edema of lungs.
3	34	July 24	Positive 16th day of disease	Aug. 14	Unknown	Aug. 16	23rd day of disease	Pneumonia	Edema of lungs.
4	57	July 14	Positive 32d day of disease	Aug. 13	Unknown	Sept. 8.	56th day of disease	Severe intestinal hemorrhages; parotitis	Toxemia.
5	26	July 15	Positive 17th day of disease	Aug. 13	Unknown	Aug. 31	47th day of disease	Pinpoint perforation 6 inches from cecum; perforation of ileum; operated August 29	Shock from operation.
6	35	Unknown	Positive 19th day of disease	Aug. 13	Unknown	Aug. 23	28th day of disease	Edema of lungs	Edema of lungs.
7	28	July 15	None	Aug. 14	None	Aug. 31	46th day of disease	Intestinal hemorrhages, Aug. 17, 18, 19; perforation, August 29; parotitis, postoperative	Toxemia and operative shock.
8	31	Unknown	None	Aug. 13	Unknown	Aug. 27	20th day of disease	Meningitis; non-hemolytic Streptococcus and Staphylococcus aureus	Meningitis.
9	31	July 24	Positive 18th day of disease	Aug. 14	None	Aug. 29	36th day of disease	Pneumonia, lobar	Pneumonia.
10	35	Unknown	Positive	Aug. 14	Unknown	Aug. 20	Unknown	Acute cholecystitis; bronchopneumonia, bilateral	Pneumonia.
11	44	Aug. 7	Positive 16th day of disease	Aug. 13	Unknown	Aug. 23	16th day of disease	Parotitis, suppurative bilateral	Toxemia.
12	38	Unknown	None	Aug. 14	Unknown	Aug. 17	Unknown	Perforation fulminant not operated	Perforation and peritonitis.
13	35	Aug. 3	None	Aug. 14	Aug. 2	Aug. 27	24th day of disease	Nephritis, toxic; pneumonia, lobar	Lobar pneumonia.
14	29	July 26	Positive 20th day of disease	Aug. 13	Unknown	Aug. 15	20th day of disease	Intestinal hemorrhages; severe pulmonary edema	Pulmonary edema.
15	35	July 2	Positive 45th day of disease	Aug. 13	Unknown	Aug. 25	54th day of disease	Nephritis, toxic; myocarditis	Nephritis, toxic; myocarditis.

TABLE II.

Case No.	Age.	Date of onset.	Blood cultures and day of disease.	Widal.	Typhoid vaccine.	Urine cultures.	Feces cultures.	Duodenal cultures and day of disease.	Complications and unusual symptoms.
16	41	July 22	28th day, neg.	39th day, pos.	None	3 neg.	3 neg.	89th day, pos.	Psychosis, toxic, August 14; cured September 26.
17	42	Aug. 12	34th day, neg. None	None	Aug. 4 Aug. 11	1 pos. 3 neg.	4 neg.	12th day, pos. 17th day, neg. None	Hematuria.
18	25	Aug. 1	18th day, neg.	None	Aug. 1	2 neg. 1 pos. 1 neg.	3 neg.	None	Furunculosis of forearm (September 15, 1918).
19	32	Aug. 2	17th day, neg.	None	Aug. 2	2 neg.	3 neg.	Neg.	Abscess of chin.
20	31	Aug. 10	9th day, neg.	None	Aug. 10	3 neg. 5 neg.	5 neg.	48th day, pos. 52d day, neg. None	Adenitis; abscesses of axillary gland (left).
21	35	Aug. 1	18th day, neg. 30th day, neg.	None	Aug. 2 Aug. 12	2 neg. 1 pos. 1 neg.	3 neg.	None	Paralysis of ulnar nerve (partial), September 20, 1918. Developed right little finger of left hand.
22	28	Aug. 6	13th day, neg. 25th day, neg.	None	Aug. 2	2 neg. 2 neg. 1 pos. 1 neg. 2 neg.	3 neg.	None	Typhoid spine; severe abscesses in lumbar muscles; ulcerative laryngitis; endocarditis; hypertrophy of heart.
23	31	Aug. 8	10th day, neg.	Pos.	Aug. 2	3 neg.	3 neg.	Neg.	Abscess left ankle, 46th to 61st day; bacteria negative; chin, positive.
24	27	Aug. 1	22d day, neg. Neg.	None	Aug. 6	1 pos. 3 neg.	2 pos. 3 neg.	71st day, pos.	Roentgenogram for gall-bladder negative.
25	20	July 27	25th day, pos. 55th day, neg.	None	None	6 neg. 6 neg.	1 pos.	66th day, pos. 73d day, neg. Neg.	Relapse.
26	27	July 24	25th day, neg.	44th day, pos.	None	4 neg.	2 neg. 1 pos. 3 neg.	None	Endocarditis, chronic.
27	28	Aug. 6	12th day, neg. 24th day, neg.	24th day, pos.	Aug. 2	2 pos. 3 neg.	Sept. 14, pos. Sept. 23, pos. Sept. 30, neg. 2 neg.	65th day, pos. 84th day, neg.	Roentgenogram for gall-bladder negative; cholecystitis.
28	27	Aug. 6	12th day, pos.	None	Aug. 1	2 pos. 2 neg. 2 pos.	.....	.....	Roentgenogram for gall-bladder negative; culture of duodenal contents remains positive 112th day of disease; cholecystitis.
29	39	July 27	22d day, pos.	None	None	Nov. 1, neg. 3 neg.	4 neg. 3 neg.	50th day, pos. Neg.	Roentgenogram of chest and abdomen negative.



30	22	Aug. 4	14th day, pos.	None	Aug. 4	8 pos.	3 neg.	.....	1. meningitis (toxemia); 2. lumbar puncture; 3. culture, spinal fluid negative. Roentgenogram for gall-bladder negative; urethritis, chronic (Neisser). Roentgenogram for gall-bladder negative.
31	36	Aug. 10	8th day, neg.	None	Aug. 2	4 neg.	1 neg. 1 pos. 3 neg.	None	
32	25	July 15	33d day, neg.	55th day, pos.	None	5 neg.	2 neg. 1 pos. 3 neg.	70th day, pos.	
33	21	July 24	24th day, neg.	44th day, pos.	None	5 pos. 3 neg. 3 pos.	3 neg.	Neg.	Phlebitis, left internal saphenous vein, on August 31; cured October 7.
34	34	....	Aug. 19, neg.	Sept. 6, pos.	None	3 neg.	2 neg. 1 pos. 2 neg.	None	Decubitus.
35	43	July 15	24th day, pos.	None	Aug. 1	3 pos. 3 neg.	2 neg. 2 neg. 3 neg.	None	Ichiorectal abscess; operated; cured.
36	21	Aug. 2	14th day, pos.	None	None	3 pos. 3 neg.	3 neg.	Neg.	Operation for intestinal perforation; none found.
37	30	July 31	19th day, neg.	Pos.	None	3 neg.	3 neg.	Neg.	Abscess of back; operated October 19, 1918.
38	19	Aug. 9	31st day, neg.	None	Aug. 2	3 pos. 2 neg. 3 neg.	1 pos. 3 neg. 3 neg.	None	Perforation; operation; secondary abscess (colon bacillus) two weeks later.
39	34	June 20	13th day, neg.	Pos.	None	3 neg.	3 neg.	Pos.	Cholecystitis; operated; culture of gall-bladder typhoid bacilli found.
40	30	July 28	40th day, pos.	Pos.	None	3 neg.	3 neg.	Neg.	Furuncle on buttocks and shoulder.
41	41	July 20	Neg.	None	Aug. 1	3 neg.	3 neg.	Neg.	Marked pulmonary congestion.
42	25	July 30	26th day, pos.	None	.....	.....	.....	.....	Syphilis, pre-tibial ulcer and positive Wassermann (November 16).
43	22	July 24	Neg.	49th day, pos.	None	3 neg.	3 neg.	Neg.	Septicemia; cured November 18, 1918.
44	30	Aug. 8	Neg.	None	Aug. 2	3 neg.	3 neg.	Neg.	Epistaxis; large decubitus (dead); intestinal hemorrhage (August 16). Syphilis, pre-tibial ulcer and positive Wassermann (November 16).
45	36	July 18	34th day, pos.	None	None	3 neg.	3 neg.	Neg.	Folliculitis, axillary, right.
46	25	July 25	Neg.	Pos.	Unknown	3 neg.	3 neg.	Neg.	Symmetrical alopecia.
47	31	July 23	Neg.	Pos.	Aug. 1	3 neg.	3 neg.	Neg.	September 9, pericostitis, left; tibia; acute; typhoid; cured November 1; September 14, pericostitis, acute; typhoid; left ulna; cured.
48	31	July 24	Neg.	Pos.	None	3 neg.	3 neg.	Neg.	Psychosis, negativism; suicidal.

Pericostitis of right clavicle, inner third (August 15); cured August 21. Parotitis; typhoid; acute; suppurative; right (August 20). Abscess; acute; suppurative; rectal (September 4); cured September 28. Decubitus (August 14); cured September 20. Abscess, acute, suppurative, dorsal (September 14); cured September 28; gain of 30 pounds on discharge from hospital.

TABLE II—CONTINUED.

Case No.	Age.	Date of onset.	Blood cultures and day of disease.	Widal.	Typhoid vaccine.	Urine cultures.	Feces cultures.	Duodenal cultures and day of disease.	Complications and unusual symptoms.
49	30	July 24	25th day, neg. 48th day, pos.	37th day, pos.	None	1 neg. 1 pos. 4 neg.	5 neg.	None	September 6, complicated appendicitis, acute; gangrene; September 6, operation; appendectomy at 1.30 P.M.; cured November 1, October 21, colitis, mucous; post-typhoidal; still present.
50	21	Aug. 7	Neg.	Pos.	None	3 neg.	3 neg.	Neg.	September 17, abscess, alveolar; acute; cured September 20.
51	42	July 15	42d day, neg.	56th day, pos.	None	2 pos. 3 neg.	3 neg.	71st day, pos. 99th day, neg.	Peritonitis 11th day; rib right posterior at costal angle on 85th day; cured 98th day.
52	48	Aug. 23	12th day, neg. 17th day, pos.	None	Aug. 7 Aug. 14 Aug. 21	3 neg.	3 neg.	48th day, neg.	Epididymitis, non-venereal. Relapse 58th to 68th day.
53	42	Aug. 6	12th day, neg.	Pos.	None	2 pos. 3 neg.	1 neg. 1 pos. 3 neg.	Neg.	Relapse 79th to 90th day. Acute cholecystitis on chronic cholelithiasis; operated October 15. Culture of gall-bladder: <i>Bacillus typhosus</i> .
54	31	July 29	22d day, pos.	33d day, pos.	None	2 pos. 2 neg. 1 pos. 2 neg.	3 neg. 8 neg.	None	August 14, psychosis; cured September 10; typhoid spine (mild); October 8, roentgenogram of spine negative; August 14, decubitus cured September 15.
55	48	Aug. 1	4 neg. 2 pos.	29th day, pos.	None	1 pos. 1 neg. 6 neg.	6 neg.	Neg.	Relapse 67th day of disease to 100th day; positive blood culture; second relapse 116th day of disease to 120th day; positive blood culture.
56	30	July 30	19th day, neg. 31st day, neg.	.....	.....	.....	.....	.....	Relapses with roseola and positive blood culture on 56th to 80th day of disease.
57	42	Aug. 7	56th day, pos. None	31st day, pos. 31st day, pos.	None Aug. 2	1 pos. 1 pos. 3 neg.	5 neg. 3 neg.	Neg. None	Phlebitis, acute in right saphenous vein.
58	38	Aug. 3	Neg.	None	Aug. 2	3 neg. 5 neg.	3 neg. 1 pos. 2 neg. 5 neg.	None	Acute cholecystitis November 2, 1918, on 91st day of disease; positive stool; symptoms disappeared 92th day of disease.
59	50	July 4	46th day, neg. 58th day, neg. 66th day, pos.	58th day, pos.	None	5 neg.		98th day, pos.	Relapse with positive blood culture; cholecystitis; gall-bladder negative in roentgenogram.

60	33	July 1	38th day, pos. 77th day, pos.	None	None	3 neg. 4 pos.	2 pos. 4 neg. 2 pos. 2 pos.	None	Ichiorectal abscess; incised; drained; 3 relapses; acute cholecystitis; marked secondary anemia.
61	52	July 15	None	51st day, pos.	None	3 neg.	1 pos. 1 neg. 1 pos.	None	Emphysema; myocarditis; toxic.
62	37	July 24	26th day, pos.	None	None	1 pos. 3 neg.	1 neg. 1 pos. 3 neg.	42d day, neg.	Asthma, bronchial (both lungs).
63	33	July 31	Neg.	3d day, pos. 2 neg., 60 day	.....	3 neg.	3 neg.	Neg.	Bronchitis, chronic.
64	33	July 28	Neg.	46th day, pos.	None	3 neg.	3 neg.	Neg.	Furunculosis; cured September 3.
65	56	July 2	Neg.	65th day, pos.	None	3 neg.	3 neg.	Neg.	September 1, myocarditis, toxic; September 23, complicated cestoda (tape-worm); Tenuis agnatus.
66	28	Sept. 9	3d day, neg. 12th day, pos.	None	Apr. 5 Apr. 14 Apr. 21	6 neg.	2 neg. 1 pos. 1 pos. 1 pos.	46th day, neg.	Relapse 32d to 42d day of disease.
67	34	Aug. 6	20th day, neg. 24th day, neg.	24th day, pos.	Aug. 9	3 neg.	2 neg.	91st day, neg.	Syphilis; tertiary; two positive Wassermanns.
68	28	Aug. 1	26th day, neg.	None	Aug. 1	2 pos. 4 neg.	1 pos.	74th day, neg.	Relapse 51st to 59th day.
69	37	Aug. 1	56th day, pos.	None	Aug. 1	4 neg.	1 pos.	75th day, neg.	Acute cholecystitis September 3. Cured September 18.
70	22	Aug. 1	28th day, neg. 40th day, pos. 26th day, neg.	29th day, pos.	None	3 neg.	3 neg.	None	Tuberculosis, pulmonary; bronchopneumonia September 7; cured October 4.
71	23	Aug. 10	36th day, neg.	None	Aug. 2 Aug. 10	3 neg.	1 pos.	64th day, neg.	Decubitus.
72	34	Aug. 1	25th day, neg. 31st day, neg.	29th day, pos.	None	3 neg.	3 neg.	59th day, neg.	Decubitus.
73	31	Aug. 1	41st day, neg. 26th day, neg.	29th day, pos.	None	3 pos. 4 neg.	3 neg.	81st day, neg.	Relapse 39th to 45th day of disease.
74	28	Aug. 1	29th day, neg.	40th day, pos.	None	1 pos. 3 neg.	3 neg.	79th day, neg.	Peritonitis August 21; 12th rib; decubitus axillary line; left; August 28, cured.
75	51	Aug. 3	23d day, pos. 70th day, pos.	None	None	1 pos. 2 neg. 1 pos. 4 neg.	4 neg.	80th day, pos. 97th day, neg.	Roentgen ray of gall-bladder negative; discharged 116th day of disease; relapse 74th day of disease; out of bed 102d day of disease; bronchopneumonia 33d day of disease; cured 58th day of disease.
76	41	July 31	4th day, neg.	43d day, pos.	None	1 pos. 3 neg.	3 neg.	69th day, pos. 98th day, pos.	Cholecystitis; roentgen ray suspicious (shadow in gall-bladder region).

Pulmonary involvement was the terminal process in 6 cases. Each of these patients suffered severe toxemia from the time of entrance, and death was predicted even before the final complication arose.

The death-rate of 8.06 per cent. was considered satisfactory for three reasons:

1. Impossibility to render proper care at Hot Springs.
2. The necessity for moving the patients fifty miles in the heat of summer.
3. The virulence of the epidemic.

Table II attempts to give concisely the list of severe cases with complications and unusual symptoms. No effort was made to include every minor complication.

A study of this table reveals the usual percentage of complications found in larger epidemics.

The varieties run almost the entire gamut from alopecia areata to typhoid spine.

The two following symptoms are not completely listed in Table II: Incontinence of stool and urine occurred in 35 patients.

Intestinal hemorrhage to a marked degree in 25 patients, though blood was present in the stools in many more instances.

Several recrudescences appeared which were not listed as true relapses.

The most interesting feature in our study of this epidemic arose in the diagnosis of our six perforations.

Not one case presented the classical symptom of sudden paroxysmal abdominal pain. Vomiting did not occur in any of the cases.

Nurses and ward aides had been instructed to notify a medical officer the moment any suggestive symptoms arose in a patient.

Our attention was called to one case by a nurse who reported that the patient complained of slight abdominal pain when she turned him in bed during the process of bathing. Examination showed no distention, no loss of liver dulness, very slight tenderness on pressure in the iliac region, but a suspicion of dulness in the flank.

There was no increase in temperature or pulse-rate, neither was there a Hippocratic facies. Blood examination revealed a leukopenia.

Operation was performed within four hours after the first symptom. A pin-point perforation was found in the ileum, four inches from the cecum, with an abundant plastic exudate over this portion of the gut.

No free fluid was present. The absence of leukocytosis in all but one patient with perforation was remarkable, and may be explained by the fact that early diagnosis was made.

The reports upon laboratory examinations and operative cases are being made in detail by Capt. Abram L. Garbat and Major Frederic Kammerer, chiefs of laboratory and surgical service, respectively.

Case 36 showed typical signs of perforation. Abdominal tenderness and distention with rise of pulse and temperature were found. The patient had an anxious expression. Surgical consultation resulted on an agreement in diagnosis. There was no leukocytosis, but this fact was not considered of importance, as other cases had been found perforated when no increase of leukocytes was observed.

Laparotomy was done and free abdominal fluid was found, with no indication of perforation.

Ulcerated Peyer's patches were readily observed through the very thin layer of gut.

A large abscess in the incision developed later in this patient and was found upon culture to contain *Bacillus typhosus*.

Involuntary urine deposited in the abdominal dressings may have been the source of the wound infection.

Fortunately this patient made a good recovery, barring the development of a sacral decubitus.

Our conclusion in regard to intestinal perforation in typhoid fever is that a diagnosis sufficiently early to offer any hopes from operative interference is an exceedingly difficult task.

The early diagnosis in practically every one of our cases forces the question as to the possibility of further reducing the death-rate from operative interference.

The service was fortunate in having the most skilful surgeons to perform the operations. Given the earliest possible diagnosis and perfect surgical technic, we feel that under no circumstances could the number of recoveries have been more favorable.

The percentage of recoveries seemed satisfactory, viz.: Two recoveries and three deaths in operated cases.

The operations in this series of cases were performed by Majors Frederic Kammerer and Alexis V. Moschcowitz.

*Appendicitis.* Case 49 presented the only incidence of appendicitis. Reference to the temperature chart indicates this patient had almost recovered from the usual course of his fever when a gradual rise of pulse and temperature occurred.

On September 2, the fortieth day of the disease, he had slightly rigid abdomen and some tenderness, with an easily palpable spleen. The rigidity subsided, but on September 6, the forty-fourth day of disease, there were rigidity and tenderness in the right lower quadrant. There was no real pain. Rectal examination revealed marked hyperesthesia, a normal prostate, no exudate in the pararectal fossa. At 1 P.M. of the same day there was pain, with increased muscular rigidity and a definitely palpable mass in the right lower quadrant.

This was accompanied by a leukocytosis of 10,200; polynuclears, 721, and then, just before operation, 16,600 and polynuclears, 631. (His previous count during the course of the fever was 4400 leukocytes with 51 per cent. polynuclears.)

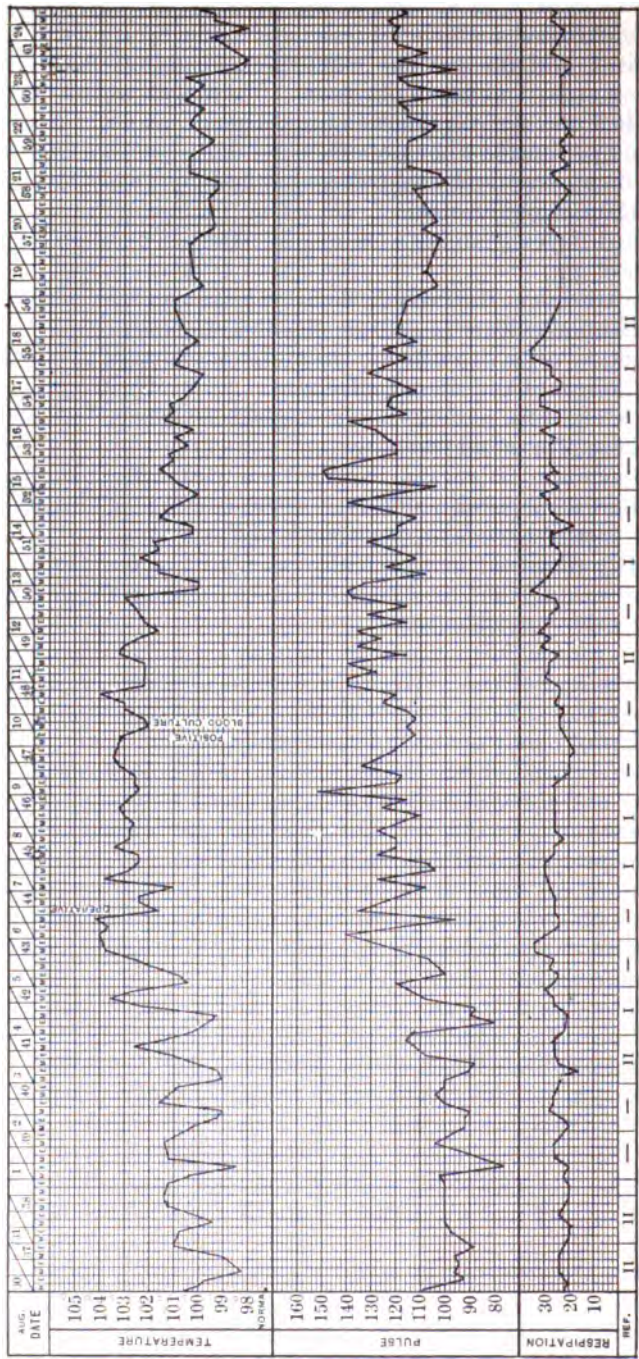


Chart of Case 49. Appendicitis complicating typhoid fever.

The diagnosis of perforation with localized abscess or appendicitis was made with the chances favoring the latter conclusion.

A median incision was made, whereupon the appendix was easily found very much inflamed and infiltrated, as was also the meso-appendix.

After removal much thickening was observed in the walls. In the middle of the appendix a round ulcer, one-half inch in diameter, was discovered. At other parts a beginning gangrene of the mucosa was seen.

The subsequent course was that of a relapse, with a positive blood culture on the forty-eighth day of the disease.

Recovery was complete except for a mucous colitis which had persisted until discharge of patient from the hospital in the last week of November, 1918.

*Cholecystitis.* The patients who developed cholecystitis offered very interesting opportunities for study. Some evidently suffered a recrudescence of a latent cholelithiasis as shown in Case 53, which was operated. A culture from the duodenum was negative for *Bacillus typhosus*, but the gall-bladder culture showed the organism of typhoid fever.

Case 58 is another undoubted instance of cholecystitis. This patient refused operation and suffered three relapses, each accompanied by an exacerbation of symptoms referable to the gall-bladder. On the ninety-first day of the disease the third relapse, with acute cholecystitis, developed. The stool became negative for *Bacillus typhosus* on the ninety-second day of the disease.

Operative interference in cholecystitis complicating typhoid fever is a questionable procedure. There seemed strong evidence in three of our most toxic patients that the cholecystitis was an incident in the disease just as is the inflammation of Peyer's glands. The decision against operation was made contrary to the opinion of the ward surgeons and the surgical service.

Fortunately the three patients recovered without surgical intervention.

Three months later there had been no recurrence of the symptoms referable to the gall-bladder. The overwhelming infection in these cases indicated that death would almost certainly follow operation.

The balance was clearly in favor of the more conservative plan. Special mention is due Case 48. The complications as seen from the table were many and varied.

His death was frequently expected. The erythrocytes at one time numbered 1,000,000. It will be noted that blood cultures, urine, stool and duodenal cultures were negative throughout. A positive Widal was found and a positive culture for *Bacillus typhosus* from the parotid gland was obtained. An operation upon an abscess was performed in the patient's bed on September 14, when death seemed imminent. In spite of this stormy illness the patient recovered his health, with a gain of thirty pounds, before leaving the hospital.

TABLE III.

Case No.	Age.	Date of onset.	Blood cultures and day of disease.	Widal.	Typhoid vaccine.	Urine cultures.	Feces cultures.	Duodenal cultures and day of disease.
77	31	Aug. 4	15th day neg.	None	Aug. 1	4 neg.	6 neg.	55th day, neg.
78	31	Aug. 3	16th day, neg.	None	Aug. 2	3 neg.	3 neg.	None.
79	48	Aug. 2	17th day, neg.	28th day, pos.	Aug. 5	3 neg.	3 neg.	Neg.
80	19	Aug. 3	15th day, pos.	None	None	3 neg.	3 neg.	53d day, neg.
81	45	Unknown	Aug. 31, neg.	None	Aug. 2	5 neg.	3 neg.	Aug. 27, neg.
82	38	Aug. 3	11th day, neg.	34th day, pos.	None	3 neg.	1 pos.	None.
83	49	Aug. 8	8th day, neg.				3 neg.	
			23d day, neg.	None	Aug. 2	3 neg.	3 neg.	Neg.
84	24	Aug. 4	15th day, neg.	None	Aug. 2	2 neg.	1 pos.	58th day, neg.
			27th day, neg.			1 pos.	4 neg.	
85	23	July 28	22d day, neg.	None	None	1 neg.	3 neg.	None.
						2 pos.		
86	29	Aug. 9	10th day, neg.	None	Aug. 2	3 neg.	3 neg.	Neg.
			22d day, neg.			3 neg.		
87	38	Aug. 5	60th day, neg.	None	None	3 neg.	3 neg.	None.
			14th day, neg.			3 neg.		
88	34	Aug. 10	26th day, neg.	None	Aug. 1	4 neg.	5 neg.	40th day, neg.
			24th day, neg.		Aug. 10			
89	30	Aug. 3	15th day, neg.	None	Aug. 17	4 neg.	3 neg.	49th day, pos.
90	32	July 1	49th day, neg.	None	Aug. 1	4 neg.	3 neg.	57th day, neg.
91	18	Aug. 6	60th day, neg.	None	Aug. 2	3 neg.	3 neg.	None.
			13th day, neg.			3 neg.		
92	34	Aug. 1	24th day, neg.	None	Aug. 7	3 neg.	3 neg.	Neg.
93	34	Aug. 2	Neg.	None	Aug. 3	3 neg.	3 neg.	Neg.
94	21	Aug. 7	17th day, pos.	None	Aug. 2	3 neg.	3 neg.	Neg.
95	21	Aug. 3	11th day, pos.	None	Aug. 3	3 neg.	3 neg.	Neg.
96	23	Aug. 5	15th day, pos.	None	Aug. 1	3 neg.	3 neg.	Neg.
			None		Aug. 9			
97	31	July 30	Neg.	38th day, pos.	None	1 pos.	1 pos.	Neg.
						3 neg.	3 neg.	



98	32	Aug. 1	17th day, neg.	37th day, pos.	None	3 neg.	3 neg.	Neg.
99	30	Aug. 4	14th day, neg.	None	Aug. 2	3 neg.	3 neg.	Neg.
100	33	Aug. 7	11th day, neg.	31st day, pos.	Aug. 2	1 pos.	1 pos.	Neg.
101	19	Aug. 1	17th day, neg.	None	July 22	3 neg.	3 neg.	Neg.
102	29	July 30	19th day, neg.	None	None	1 pos.	5 neg.	Neg.
103	33	Aug. 1	17th day, pos.	None	Aug. 2	3 neg.	3 neg.	Neg.
104	46	Aug. 5	13th day, pos.	None	None	1 pos.	1 pos.	Neg.
105	27	Aug. 1	17th day, neg.	37th day, pos.	None	3 neg.	3 neg.	Neg.
106	37	Aug. 9	10th day, neg.	None	Aug. 1	2 pos.	2 pos.	Neg.
107	35	July 24	12th day, neg.	51st day, pos.	Aug. 7	3 neg.	1 pos.	Neg.
108	31	Aug. 3	15th day, neg.	36th day, pos.	Aug. 4	1 pos.	3 neg.	Neg.
109	19	July 30	19th day, neg.	32d day, pos.	None	3 pos.	4 neg.	Neg.
110	24	Aug. 10	27th day, neg.	None	None	2 neg.	2 pos.	None.
111	29	Aug. 1	8th day, neg.	None	Aug. 1	1 pos.	3 neg.	None.
112	44	Aug. 3	18th day, neg.	None	Aug. 1	3 neg.	4 neg.	None.
113	41	Aug. 3	15th day, neg.	Pos.	Aug. 5	3 neg.	2 neg.	Neg.
114	33	Aug. 2	27th day, neg.	34th day, pos.	Aug. 1	2 pos.	2 pos.	63d day, neg.
115	40	Aug. 10	8th day, neg.	None	None	1 neg.	3 pos.	None.
116	29	July 24	Neg.	30th day, pos.	Aug. 2	3 neg.	4 neg.	None.
117	29	July 31	33d day, pos.	None	Aug. 4	1 pos.	1 pos.	Neg.
118	32	July 28	Neg.	Pos.	None	3 neg.	3 neg.	Neg.
119	30	July 26	Neg.	Pos.	Aug. 4	3 neg.	3 neg.	Neg.
120	24	July 24	Neg.	None	None	3 neg.	3 neg.	Neg.
121	41	July 25	18th day, neg.	Pos.	None	3 neg.	3 neg.	Neg.
			29th day, pos.					

TABLE III—CONTINUED.

Case No.	Age.	Date of onset.	Blood cultures and day of disease.	Widal.	Typhoid vaccine.	Urine cultures.	Feces cultures.	Duodenal cultures and day of disease.
122	37	Aug. 11	7th day, pos.	None	Aug. 3	3 neg.	3 neg.	Neg.
123	25	July 2	Neg.	Poa.	Aug. 11	3 neg.	3 neg.	Neg.
124	23	July 23	None	44th day, pos.	None	4 neg.	4 neg.	Neg.
125	25	July 20	58th day, neg.	58th day, pos.	None	3 neg.	3 neg.	76th day, neg.
126	40	Aug. 5	Neg.	Poa.	None	3 neg.	3 neg.	Neg.
127	23	Aug. 5	Neg.	None	Aug. 4	3 neg.	3 neg.	Neg.
128	37	Aug. 23	27th day, pos.	None	None	3 neg.	3 neg.	Neg.
129	22	Aug. 7	9th day, pos.	None	Aug. 1	3 neg.	3 neg.	Neg.
130	39	July 24	26th day, pos.	None	None	3 neg.	3 neg.	Neg.
131	33	July 24	26th day, pos.	None	None	3 neg.	3 neg.	Neg.
132	18	July 24	Neg.	Poa.	None	3 neg.	3 neg.	Neg.
133	22	July 22	Neg.	Poa.	None	3 neg.	3 neg.	Neg.
134	33	July 25	Neg.	Poa.	None	3 neg.	3 neg.	Neg.
135	44	Aug. 2	2 neg.	Poa.	July 27	1 pos.	3 neg.	None.
136	23	July 20	None	None	None	4 neg.	3 neg.	71st day, neg.
137	38	Aug. 10	None	None	Aug. 7	3 neg.	1 pos.	53d day, neg.
138	31	Aug. 4	22d day, neg.	26th day, pos.	Aug. 14	3 pos.	2 neg.	76th day, pos.
			28th day, neg.		None	3 neg.	1 pos.	95th day, neg.
139	31	Aug. 14	22d day, neg.	None	Aug. 1	2 pos.	3 neg.	84th day, pos.
140	60	Aug. 16	None	None	Aug. 10	3 neg.	1 pos.	101st day, neg.
141	25	Aug. 4	22d day, neg.	26th day, pos.	Aug. 9	2 pos.	5 neg.	59th day, neg.
			28th day, neg.		Aug. 16	4 pos.	3 neg.	70th day, neg.
			33d day, neg.		Aug. 4	3 neg.		
142	30	Aug. 8	44th day, neg.	None	Aug. 1	3 neg.	3 neg.	25th day, neg.
143	27	Aug. 1	18th day, pos.	None	Aug. 4	3 neg.	3 neg.	58th day, neg.
144	24	Aug. 1	28th day, neg.	29th day, pos.	Aug. 11			
			30th day, neg.		Aug. 1	1 pos.	3 neg.	76th day, neg.
145	24	Aug. 10	16th day, neg.	None	Aug. 1	3 neg.	3 neg.	67th day, neg.

146	24	Aug. 6	12th day, neg. 24th day, neg. 22d day, neg.	24th day, pos. 33d day, pos. 40th day, pos. None	Aug. 2 None None Aug. 3	3 neg. 1 pos. 3 neg. 1 neg. 1 pos. 3 neg. 3 neg. 3 neg.	47th day, neg. 61st day, neg. 55th day, neg. None.
147	30	July 28	24th day, neg. 22d day, neg.	12th day, pos. 30th day, neg. 40th day, neg. None	Aug. 2 Aug. 6 Aug. 3 Aug. 10	3 neg. 5 neg.	37th day, neg. 74th day, neg.
148	28	July 28	24th day, neg. 16th day, neg.	12th day, neg. Pos.	Aug. 2 Aug. 6	3 neg. 4 neg.	42d day, neg.
149	53	Aug. 3	12th day, neg. 16th day, neg.	None	Aug. 3 Aug. 10 3 in Aug. Aug. 2 None None	3 neg. 3 neg. 3 neg. 2 neg. 1 pos. 3 neg. 3 neg.	None. 56th day, neg. None. None. None.
150	40	Aug. 6	12th day, pos. 30th day, neg. 40th day, neg.	36th day, pos. None	None	1 pos. 3 neg. 3 neg.	Neg.
151	40	July 15	4 neg. 2 neg. 18th day, neg. 14th day, pos.	42d day, pos. 70th day, neg. 74th day, pos. None None None	June 24 Aug. 1 Aug. 9 Aug. 2 Aug. 1 Aug. 8 Aug. 1 Aug. 9 Aug. 7 Aug. 15 Aug. 2	3 neg. 2 pos. 3 neg. 1 pos. 4 neg. 3 neg. 1 pos. 3 neg. 3 neg. 3 neg. 2 pos. 3 neg.	80th day, neg. None.
152	44	Aug. 13	None	None	Aug. 2	3 neg.	69th day, neg. 63d day, neg. None.
153	52	July 24	8th day, pos. 28th day, neg. 37th day, pos. 20th day, neg.	None	Aug. 1 Aug. 8 Aug. 1 Aug. 9 Aug. 7 Aug. 15 Aug. 2	3 neg. 3 neg. 3 neg. 3 neg. 3 neg. 3 neg. 3 neg.	71st day, neg. 71st day, neg. 44th day, neg. 82d day, neg.
154	62	Aug. 6	24th day, neg. 31st day, neg. 26th day, neg.	None	Aug. 2	1 pos. 3 neg.	52d day, neg.
155	25	Aug. 1	25th day, pos.	None	Aug. 2	3 neg.	52d day, neg.
156	35	Aug. 4	43d day, neg.	None	Aug. 1	3 neg.	Neg.
157	25	July 1	None	45th day, pos.	Aug. 2	3 neg.	
158	24	July 25	8th day, pos. 28th day, neg. 37th day, pos. 20th day, neg.	None	Aug. 2	3 neg.	
159	32	Aug. 1	24th day, neg. 31st day, neg. 26th day, neg.	None	Aug. 1	3 neg.	
160	35	Aug. 6	25th day, pos.	None	Aug. 1	3 neg.	
161	38	Aug. 2	43d day, neg.	None	Aug. 1	3 neg.	
162	55	Aug. 15	None	None	Aug. 15	3 neg.	
163	39	Aug. 1	37th day, neg. 41st day, neg. 45th day, neg. 36th day, neg.	None	Aug. 15	3 neg.	
164	37	Aug. 1	None	None	July 15	3 neg.	
165	50	Aug. 15	None	None	Aug. 14	3 neg.	
166	37	July 15	37th day, neg. 41st day, neg. 45th day, neg. 36th day, neg.	None	Aug. 2	3 neg.	
167	39	Aug. 14	None	None	Aug. 4	3 neg.	
168	22	Aug. 2	None	None		3 neg.	
169	22	Aug. 4	22d day, neg.	None		3 neg.	

24th day, neg.  
37th day, neg.  
47th day, neg.

3 neg.  
5 neg.  
3 neg.  
3 neg.

3 neg.  
1 pos.  
3 neg.  
1 neg.  
1 pos.  
3 neg.  
3 neg.  
3 neg.

Aug. 2  
None  
None  
Aug. 3

24th day, pos.  
33d day, pos.  
40th day, pos.  
None

12th day, neg.  
24th day, neg.  
22d day, neg.

Aug. 6  
July 28  
July 28  
Aug. 3

24  
30  
28  
53

TABLE III—CONTINUED.

Case No.	Age.	Date of onset.	Blood cultures and day of disease.	Widal.	Typhoid vaccine.	Urine cultures.	Feces culture.	Ducodenal cultures and day of disease.
170	22	Aug. 17	20th day, pos.	None	Aug. 1	1 pos.	4 neg.	60th day, neg.
171	46	Aug. 14	23d day, neg.	None	Aug. 8	3 neg.	3 neg.	52d day, neg.
172	45	July 24	30th day, neg.	None	Aug. 2	1 pos.	3 neg.	None.
173	39	Aug. 15	33d day, neg.	None	Aug. 10	3 neg.	3 neg.	57th day, neg.
174	28	July 24	36th day, neg.	None	July 12	1 pos.	1 pos.	25th day, neg.
175	37	Aug. 12	None	None	Aug. 7	3 neg.	3 neg.	57th day, neg.
176	34	July 21	30th day, neg.	None	Aug. 4	1 pos.	3 neg.	83d day, neg.
177	27	Aug. 1	35th day, neg.	50th day, pos.	Aug. 5	3 neg.	3 neg.	36th day, neg.
178	32	July 15	25th day, pos.	None	None	3 neg.	5 neg.	Neg.
			33d day, neg.	None	Aug. 4	1 pos.	3 neg.	None.
179	22	Aug. 3	8th day, neg.	27th day, pos.	None	3 neg.	3 neg.	55th day, neg.
180	29	Aug. 14	27th day, neg. *	None	Aug. 1	1 pos.	3 neg.	61st day, neg.
181	19	Aug. 11	Neg.	19th day, pos.	Aug. 9	3 neg.	3 neg.	46th day, neg.
182	46	Aug. 7	15th day, neg.	None	None	1 pos.	5 neg.	68th day, neg.
183	45	Aug. 4	19th day, neg.	None	Aug. 7	4 neg.	1 pos.	None.
			11th day, pos.	None	Aug. 4	1 neg.	3 neg.	None.
184	32	Aug. 16	None	None	Aug. 4	3 pos.	4 neg.	None.
185	47	Aug. 18	None	None	Aug. 12	1 pos.	1 pos.	None.
186	21	Oct. 25	21st day, pos.	None	Aug. 22	4 neg.	3 neg.	None.
					Aug. 2	3 neg.	.....	
					Aug. 10	3 neg.		
					Aug. 17			
					Immunisation completed Oct. 30, 17			

Bronchitis was observed so frequently that his phenomenon may not be considered a complication but a most frequent symptom.

Bed-sores were present in 4 of the 8 cases on admission to the hospital. Dakin's solution was used in two cases, but healing seemed to result more rapidly by the older methods of treatment.

The old view that recrudescences and relapses are caused by starvation is refuted in this series of cases.

Table III represents the cases which were uncomplicated. As will be observed by a study of the outline, a certain number of cases have been proved bacteriologically. The majority of the cases were proved clinically typhoid fever in this hospital. A small number who were ill at Hot Springs arrived at this hospital without clinical records, and from all accounts have had typhoid fever.

Typhoid vaccination was given in many cases during the incubation period of the disease. We were unable to observe any amelioration of the symptoms among such patients.

Both ward aides who contracted the disease had rather a severe infection in spite of the immunization given several months previously. This illustrates the fact that vaccination confers only a relative immunity and does not protect against an overwhelmingly large dose of typhoid bacilli.

Nine cases of true relapse and several of recrudescences were certainly not due to undernutrition, as will be seen in the discussion of dietetic treatment.

**TREATMENT.** Upon the entrance of the patients to the hospital the following general line of treatment was agreed upon among the ward surgeons after consultation with the chief of the service.

The following notice was thereupon posted in the chart rooms:

#### SUGGESTIONS IN TREATMENT OF TYPHOID CASES.

*Severe Hemorrhages.* No food by the mouth; ice-cap over the abdomen; small amount of ice by the mouth; in severe cases hypodermoclysis. When associated with anemia horse serum is to be used, atropin sulphate 100 gr. to be administered every six hours hypodermically.

*Marked Delirium.* (a) Sodium bromide; (b) codein; (c) ice-pack; (d) if above measures are not effectual, lumbar puncture should be done.

*Constipation.* Bowels should be moved every other day by enema; small doses of cascara may be employed when necessary.

*Cardiac Asthenia.* (a) Digitalen; (b) camphorated oil hypodermically.

Nurses and ward men should be instructed to report at once patients who have sudden rise or drop in temperature, severe pain in the abdomen or sudden relief of delirium.

With very few alterations, this plan was followed.

The necessity for treatment of constipation was very noticeable. The majority of the patients showed difficulty about evacuations and very few cases of diarrhea were noted.

One ward surgeon used spiritus frumenti every three hours for one week upon his own responsibility. It was found in 10 patients under his care that tachycardia developed during convalescence when they were first allowed out of bed. Convalescence was thus prolonged. Overstimulation seemed to have caused this phenomenon, as this symptom was not observed in other wards.

Cold sponges were employed to counteract the hyperpyrexia, which method seemed quite as successful as the method of tubbing.

*Dietetic Treatment.* A diet of 1900 calories, consisting of milk, coffee, oatmeal gruel, custards, whey, broth and eggs, was given during the severest periods of illness. As soon as seemed compatible with safety a higher nutritive combination was employed. This second diet contained 2300 calories.

The convalescent diet consisted of 3190 calories. The latter diet exceeded the ration allowance for patients in this hospital by 22 cents, but the excessive cost seemed amply repaid by the rapid convalescence of the patients.

All patients soon reached their normal weight, some having gained by the time of discharge twenty to thirty pounds.

To the writer, whose experience in the treatment of typhoid fever dates back to the time of starvation methods, this dietetic *régime* seemed a great advantage.

The development of perforation did not exceed that of former years, but the number of patients with severe toxemia was rather high.

The severity of the epidemic described may, however, account for the latter fact.

The laboratory findings by Capt. Garbat must revolutionize our ideas as to when a convalescent typhoid patient may be discharged as cured if he is not to be a factor in a further distribution of the disease.

At least four negative stool and urine cultures at intervals of six days should be demanded in each case.

Before precautions in regard to stools are discontinued each patient should show a negative duodenal culture. Twenty-one roentgenograms were taken in patients with symptoms suggestive of cholecystitis and in those with positive duodenal cultures. Although Capt. Donald S. Childs's technic is an excellent one, only 2 patients exhibited suspicious shadows in the right upper quadrant.

Finally, the results of the treatment in these German aliens amply justified their transfer from Hot Springs to this hospital.

The causes of the epidemic have not been discussed in this contribution, as a complete report upon the subject was rendered the Surgeon-General's Office by Lieut.-Colonel Weed.

## RECAPITULATION OF TABLES I AND II.

Abscess (alveolar, 1; ankle, 1; back, 1; chin, 1; ischiorectal, 3)	7
Adenitis, axillary	1
Alopecia, areata	1
Appendicitis (gangrenous)	1
Asthma	1
Bronchopneumonia	3
Bronchitis (chronic)	1
Cholecystitis (operated, 2)	11
Decubitis (extensive)	8
Edema of lungs	2
Endocarditis	2
Epistaxis (severe)	1
Furunculosis	4
Hematuria	1
Meningitis	3
Myocarditis	3
Nephritis	3
Paralysis (ulnar)	1
Parotitis (deaths, 2; recoveries, 2)	4
Perforation (deaths, 3; recoveries, 3)	6
Periostitis	4
Phlebitis	2
Pneumonia	2
Psychosis	3
Relapses	9
Typhoid spine	2
Tuberculosis pulmonary	1

## RECAPITULATION OF TABLES I, II AND III.

Ages: Youngest, 18 years; oldest, 60 years; average, 33.18 years.

Blood Cultures: Positive, 54; percentage, 29.

Vaccination: No vaccination against typhoid	74
One vaccination against typhoid	73
Two vaccinations against typhoid	20
Three vaccinations against typhoid	6
Not known	13
	<hr/>
Total vaccinated	186
	99

Cases proved typhoid fever by laboratory (either positive blood culture, urine, stool or duodenal culture or Widal in cases having received no vaccination), 141, or 75.8 per cent.

In conclusion, an appreciation of the earnest, untiring zeal shown by the entire personnel engaged in the care of the typhoids is hereby acknowledged.

**SOME MEDICAL IMPRESSIONS OF THE WAR.**

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THE impressions received during nineteen months of overseas service, all but two months of it in France, a part of it in the advance sector, zone of the advance and a part of it in base sectors, are so manifold and kaleidoscopic that it is somewhat difficult to evaluate their relative importance. In the following sketchy discourse an attempt will be made to briefly allude to those aspects which appeal more especially to the internist.

I. TRENCH FEVER. This new, specific, definitely established disease of unknown etiology was the greatest incapacitating factor in the British Army. Transmission by the body louse, both by its bite and by its excreta (when inoculated by way of cutaneous scratching), is universally accepted. It was virtually unknown in the A. E. F. except in the experimental volunteers. It is characterized by sudden onset, with chill, weakness, periods of usually intermittent and recurrent pyrexia ( $103^{\circ}$  to  $104^{\circ}$  F.), and pain in the bones, muscles and fascia. In two-thirds of the cases prodromes in the form of headache and body pains precede the attack from one to ten days. The nocturnal shin pains are so characteristically severe and constant that everyone thinks at first of secondary syphilis. Frontal and postorbital headache is common. A macular eruption much like the rose spots of typhoid fever occurs, on the second day, in about half of the cases. A ward full of trench-fever patients is one of the gloomiest spots on earth, in contradistinction to the cheer which invests the surgical pavilions. Relapses are very common and sequelæ, such as the effort syndrome, frequent.

Experimental investigations have shown that the disease is a specific entity, due to a filterable virus, which is present especially in the plasma of the blood. The infective agent may also be found in the urine and sputum of trench-fever patients.

Drugs as well as local applications are ineffectual even as palliatives of pain and insomnia. Major J. E. Sweet has had seemingly encouraging, almost brilliant results from a curative standpoint from the intravenous administration of collargol, although the total number of cases thus treated was, owing to the scarcity of the drug, small.<sup>1</sup>

II. TRENCH FOOT. This term has been applied to the vasomotor, nervous and trophic disturbances of the feet of soldiers exposed to wet trenches and cold, damp air, especially during physical inactivity,

<sup>1</sup> For fuller information see Trench Fever, Report of American Red Cross Research Committee, Oxford University Press, 1918.



and if tight shoes or puttees are worn. Sometimes the hands, nose and ears are similarly affected.

The lesions vary from numbness and simple swelling to severe pain and tenderness and cyanosis and gangrene. Investigations made by Major J. E. Sweet, Lieut. H. B. Wilmer and myself at No. 16 General Hospital B. E. F. disclosed the interesting fact that with the subject in the horizontal posture, blood-pressure was higher in the legs than in the arms. This difference, which ranged between 5 and 25 mm. Hg., disappeared as the case improved and could be used to separate malingerers from cases of real hyperesthesia without demonstrable visible changes. We were also able to relieve pain and hasten cure by the administration of sodium iodide (20 grains t. i. d.). Just how the iodide acts is not known. It was thought that it might be by stimulating the thyroid gland, but the administration of thyroid extract failed to yield similar results. Wassermann tests were not available, but the response to the iodide medication was too universal to be explained by the fact that we had happened upon syphilitic cases.

III. INFLUENZA. Influenza apparently differed in nowise from that which occurred in the United States. In fact, some of our worst cases were those who developed the infection on board the overcrowded transports en route to England and France.

At the front last August, before the influenza epidemic appeared, one encountered hundreds of cases of what came to be known as "three-day fever," a curious and very infectious condition which in the Toul sector, for lack apparently of a definite name, was designated as "plufus." This infection, which bore some slight resemblance to dengue, was characterized by sudden onset, with very severe pain in the back, coryza, bronchitis and conjunctivitis. The fever usually ran a three-day course, sometimes terminated by crisis, and was usually followed by prompt convalescence. Bacteriological studies failed to disclose anything unusual or characteristic. Occasionally bronchopneumonia occurred as a complication. Whether this disease was really mild influenza, first manifesting itself in our army, is still unsettled.

Definite influenza appeared later and was especially fatal among those who did not promptly report at sick call but who remained at their post of duty for a day or two while feeling badly.

At ports of debarkation the most harrowing scenes were witnessed when some of the large transports arrived. One transport brought in 500 cases of pneumonia, and it was reported that the "Olympic" alone on one occasion landed 1500 cases of influenza in England, having had many deaths at sea. On another occasion the "Leviathan" brought 1200 cases into Brest, and was reported to have had over 100 corpses on board.

The institution of masking was, however, entirely satisfactory, and ships upon which this procedure was rigidly carried out had practically no influenza.

IV. TRAUMATIC HEMOTHORAX. Wounds of the chest, accompanied as they nearly always were by hemo- or hemopneumothorax presented many points of interest to the internist, who attended them jointly with the surgeon. In some hospitals these cases were sent to special wards on the medical service, the surgeon being called in when needed. Only about two out of ten chest cases which have reached the evacuation hospital require surgical intervention, for unless infection has occurred, aspiration of the intrapleural blood is generally all that is required. Indeed, a through-and-through gunshot wound of the chest, made by a clean bullet, is, unless it happens to pierce a vital organ or a large vessel, one of the most benign wounds of the war.

The physical signs noted in these cases differ greatly from those encountered in the pleural effusions of civil life. Nearly always the diaphragm is high on the affected side. This produces a tympanitic note at a level above that at which such a sound is normally encountered. Tympany over an injured lung is very common. It may result from (1) free intrapleural air; (2) relaxed lung; (3) high abdominal viscera; (4) gas bacillus infection.

Hemothorax or pulmonary collapse, or both, may occur without penetration of the chest wall. Indeed, these conditions may be contralateral—that is, they may occur on the opposite side to that of the injury. The existence of such a contralateral collapse, while rare, has been definitely established, but it should not be evoked to explain physical signs unless other causes can be eliminated with reasonable certainty.

One of the commonest mistakes made by one who is not familiar with war wounds is that of diagnosing a pneumonia on the unwounded side. Such a pneumonia is distinctly rare, but the physical signs of consolidation are very commonly present. The bronchial breathing and other signs are usually due to compression of the injured or uninjured lung by a hemothorax or a displaced mediastinum. Sometimes they are due to atelectasis. Fever and leukocytosis may, of course, occur without pneumonia.

Cardiac displacement is one of the most important criteria for judging the location and size of an effusion. Let me emphasize location, for missiles often follow devious courses and the effusion, or the largest effusion, if both sides are involved, may be on the side opposite to that of the wound of entrance. Sudden and marked cardiac displacement, especially if occurring several days after the injury, and if associated with an increase of tympany and dyspnea, points very suggestively to gas bacillus infection. The sudden appearance of marked jaundice makes one think of hepatic injury, but this symptom may occur without any injury to the liver as a result of gas bacillus hemolysis.

It is often extremely difficult to decide whether the diaphragm has been injured or penetrated. Abdominal rigidity and pain, with

nausea and even vomiting, are all symptoms which may occur from chest wounds if the diaphragm is irritated, in the entire absence of peritoneal infection or injury.

If the hemothorax is large it is well to aspirate as much blood as possible after two or three days have elapsed from the time of injury. The needling should, however, be done high up and in the anterior axillary or even midclavicular line. If the usual posterior site, at the scapular angle, is chosen a dry tap almost invariably results. This is due to the fact that the thick, fibrinous, corpuscle enmeshing portion of the blood accumulates behind; while the thin, serous, dark red, fluid portion is nearly always found anteriorly.

V. GAS POISONING. Although many different gases were used either singly or in combination the vast majority of cases met with belonged to one of two types:

- (a) *Suffocative*: chlorin, phosgen, diphosgen, orychlorcarbon.
- (b) *Vesicating*: dichlorethylsulfide, dichlormethyl-ether.

The most commonly used were diphosgen and dichlorethylsulfide ("mustard gas").

A field hospital full of freshly and badly gassed men is, in the estimation of all who have had an opportunity of seeing it, the most horrible and ghastly sight of the war. Even the man who has received multiple and severe wounds, when he has been splinted, put to bed, and given his morphin, is relatively comfortable; but to see a hundred or more men, hale and hearty a few hours before, slowly strangling to death from pulmonary edema, with gradually increasing dyspnea, cyanosis and pallor, making futile efforts to expectorate and to assist their breathing by volitional effort and muscular contortions, until exhausted they pass from semidelirium into stupor, collapse and death, is a never-to-be-forgotten sight. A sight which makes one clench one's teeth and curse the Hun who started this dastardly infamy.

This is phosgene!

But can nothing be done? Yes! the cyanotic cases are promptly bled one pint, sometimes two. The ward looks like a shambles, because in hurrying from bed to bed, twenty to thirty in a row, the spurting blood has left its trace upon bed and floor and linen. Meanwhile, oxygen is being administered to greedy mouths while hands are loath to loose the bag when their five minutes of respite are over. For never are there enough bags for all, and the precious gas we must not waste, for it has been no small task to bring these great iron tanks up to the front. Opium we dare not use for it checks an oft life-saving cough. But the gray cases, what of them? Lying about with clammy skin, too weak to move or even care. Some venturesome spirits say that one should bleed and then transfuse, but most that we should meddle not.

Digitalis intravenously often helps. This with timely bleeding has snatched many a man from the jaws of death. No one who

has seen these measures tried longer doubts the therapeutic efficacy of phlebotomy.

But let us shift the scene. We are now in a base hospital, sixty miles from the front. At midnight we are to receive a convoy of 400 men who were gassed thirty-six hours earlier. Men who lay in an evacuation hospital for only a few hours and were sent down to us because a "big show" was staged, and since they seemed only moderately gassed, there was no room for them near the front. The train arrives at 3 A.M. The station party—hospital corps men—who for three hours have been trying to keep from freezing by pacing the station platform, help unload the train; and now ambulances in monotonous succession roll up to the receiving ward, unload and return for more. But what manner of patients are these? Their faces red and blistered, their eyes swollen shut, edematous and weeping pus, with photobia so intense they shield their closed eyelids from the glare of the acetylene flame which lights our portals. The covering blankets are soiled with pus, blood and respiratory mucosa coughed up or flowing from the nostrils, for the gas has slowly done its destructive work.

Once in the ward, off come the clothes, and with them often large areas of skin from blistered spots on back, buttocks and genitalia. Fever is present, with dyspnea, chest pain, mild delirium and incessant cough, which, coming uncontrollable from nigh every bed, drives the night nurse into despair. These patients die a lingering death from bronchopneumonia days or weeks after their gassing. In their terminal delirium they fight their battles o'er; curse the Hun or call to loved ones at home.

This is "mustard gas!"

And what can we do? But little, save to remove the clothes which hold the gas, bathe with soapy water, which takes it up, and attempt to ease with steam inhalations and morphin.

Mustard gas was an extremely efficient weapon. It had but little odor, no immediate irritative properties and it soon paralyzed the sense of smell. Areas over which it had been sprinkled from the bursting shell were dangerous, if not absolutely untenable, for days. Even the continuous wearing of masks did not prevent the body burns. A man might sleep in an infested dug-out for hours without being conscious of gas, and yet on waking be fatally poisoned. Then, too, although the actual mortality rarely exceeded 5 per cent., men were incapacitated for weeks and months. Permanent damage to the eyes was practically unknown and the danger of subsequent tuberculosis greatly overrated. It is more than likely that such gassing is capable of activating a latent or healed tuberculosis, but most of the cases who were gassed sufficiently to produce a demonstrable bronchopneumonia died of that condition. In so far as the respiratory tract is concerned, horses suffered much less than men, but one often saw very pathetic animals being led down

the roads, with low hanging heads and badly blistered fetlocks and genitalia.

As I look back in my memory I see many such scenes as I have fatuously tried to describe. I see hospital orderlies who have spent the day scrubbing floors, cleaning up orange peels and cigarette refuse, serving meals, washing dishes and wondering what the next inspection will bring forth, only to pass the night in carrying litters, checking men's personal belongings, recording admissions, transporting muddy uniforms to the sterilizer or removing corpses to the morgue. I see medical officers who have spent their days in operating, dressing wounds, writing histories, auscultating chests, censoring letters and making far too many reports in triplicate, only to spend their nights in receiving new patients and often vainly attempting to comfort the comfortless. In civil life we used to think our hospital services heavy when we had six or eight new cases a day. At No. 16 General Hospital it was no uncommon occurrence for an officer to learn by way of breakfast pleasantries that 80 new cases had been admitted to his service during the night and that papers would have to be prepared for the evacuation by convoy of 40 others during the afternoon. During my ten months' stay at this institution 17,000 cases were admitted and discharged. Nor do I forget the patient toilers in the laboratory, as a result of whose labors pathogenic organisms were identified and great gaping wounds were closed and promptly healed.

As I look back I see in my mind many images in gray, walking the wards at the base hospital, treading through the aisles of a hospital train or wading through the tented mud of the field or mobile hospital near the front. Images which toiled by day or night, regardless of fatigue, discomfort or the bombing Hun, often with sleep forgotten, and the irritation which goes with exhaustion kept well in the background. Images which I honestly believe did more to encourage self-control, to make home seem near and to make suffering bearable to the sore-tried, though well-nigh always uncomplaining gassed or wounded man. I shall never forget how a certain field hospital, overburdened with 600 patients and with a hopelessly inadequate force of "green" "corps" men, who had never taken a temperature or made a bed, was cleaned, ordered, chastened and transformed in a few days into something like what a hospital should be by the arrival of twenty-four American trained nurses. Nor do I forget that a certain division surgeon against whose protest these women had been sent to the advanced zone, frankly changed his mind, honorably ate his words and departed with his division after having moved Heaven and earth to retain these same nurses as a part of his divisional medical equipment.

And in my recollection I also see the chaplains of the army. "Padres" we learned to call them from the British, and often did, as the term seemed more fitting, for fathers they truly were, as they

mingled in the sports and jests, shared the sorrows and the heartaches of the sorely afflicted; too often later, and with heartaches of their own, leading the little burial party to the nearby soldiers' cemetery.

Nor can I forget the fostering care of the British Y. M. C. A., under whose auspices and at whose expense the poor old fathers and mothers from the sleepy villages of England, who had a severely wounded son in the hospitals of France, were brought across the channel, rushed across the land by motor and arrived twelve hours after leaving London, bewildered in a strange country, overwhelmed by unaccustomed sights, but undyingly grateful to see their son and know what care he was receiving.

Now when one asks me as many do: "Was not your experience medically of great value to you? I wonder if it was? We learned to diagnosticate and treat gassed men and we gained some knowledge regarding traumatic hemothorax, trench feet and trench fever. But little of all this has a postbellum application. We handled disease, especially infectious disease, as in civil life, and we treated psychoneuroses by explanation, suggestion and reëducation. Again—nothing new. Of spirochetal jaundice one saw but little, and that trench nephritis was a new and definite entity one has yet to be convinced. On the other hand, many of the refinements of modern diagnosis and treatment had, by stress of circumstances or for lack of supplies and facilities, to be foregone.

No one, I think, could go through the last twenty months of the war abroad without being profoundly influenced and broadened; but that the internist profited by the acquisition of professional experience and knowledge is, to say the least, doubtful.

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## TESTS OF THE FUNCTIONAL CAPACITY OF THE CIRCULATION.

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THIS report is based upon studies made on soldiers between the ages of twenty and thirty years recruited into the army at Camp Zachary Taylor, Ky. The observations were all carefully recorded and were compiled as a mass of figures. An analysis is here attempted to discover the results and their collective value.

Studies were made upon the pulse-rate, systolic and diastolic blood-pressure in the seated posture and repeated with the patient standing and again after exercise. The blood-pressure was measured

by the auscultatory method, using a vertical mercury manometer and a wide cuff. Hopping 100 times on one foot was the exercise used, that being the one prescribed for the examination of the soldier. In most cases a series of observations was made and repeated and the average figures calculated. Any discrepancies or peculiar findings will receive particular annotation.

In all 233 cases were observed. They are arranged according to their clinical diagnoses into the following groups:

	Cases.
Normal heart . . . . .	124
Tachycardia, simple . . . . .	32
Tachycardia, paroxysmal . . . . .	5
Tachycardia, thyrotoxic . . . . .	9
Neurocirculatory asthenia . . . . .	28
Nephritic hypertension . . . . .	11
Mitral regurgitation . . . . .	12
Aortic regurgitation . . . . .	5
Sinus bradycardia . . . . .	2
Auricular flutter . . . . .	1
Heart drawn to left by chronic adhesions . . . . .	1
Heart drawn to right by chronic adhesions . . . . .	1
Congenital dextrocardia . . . . .	1
Patent ductus arteriosus . . . . .	1
	<hr/> 233

**NORMAL EFFECT OF CHANGE OF POSTURE UPON THE PULSE-RATE.** Donnell showed that the pulse-rate is normally slower in the recumbent than in the erect or semierect positions. Schapiro and Cabot and Bruce found that the normal difference disappears when the heart is seriously weakened. Geigel concludes that a variation of pulse-rate above 30 between lying and standing or an inversion of the normal relationship indicates weakened heart function. It must always be remembered that psychic factors may considerably disturb the correctness of the estimate in any particular case.

In our group of 124 soldiers with clinically normal hearts the pulse-rate rose an average of 16 beats from the seated to the erect posture. The variations above and below the average were comparatively slight; the maximum rise was 28 in a few cases and the minimum in one case was 0. As one peruses the list the most frequent figures are 12, 18 and 24. Whenever a variation of 30 or over occurred in this series of normal cases, subsequent tests proved that this was not constant and was probably due to adventitious influence.

**NORMAL EFFECT OF EXERCISE UPON THE PULSE-RATE.** The variation of pulse-rate following exercise and its functional significance was the earliest test of the circulation to be studied. Mendelsohn and Graüpnier showed that the longer the time it took for the heart to return to its previous rate after a measured amount of work the less efficient it was. Mendelsohn asserted it as a principle that the greater the amount of work done with prompt return to the normal rate the greater the functional capacity of the heart.

The amount of work should be considered of relative value only. Absolute amounts of work cannot be laid down as the normal for any person because the capacity for work varies with the weight, muscular development and general makeup of the individual.

The "hopping test" used in this study is a modification of the stair-climbing test commonly employed, and when standardized is of equal service with the latter. It has the obvious defect that the actual amount of work performed by the individual cannot accurately be computed. However, in performing the prescribed exercise we considered that the body weight is raised an average of about three inches, or one-quarter of a foot. The toes are raised from the ground perhaps one inch and the knee is raised about two inches. Taking the average weight as 150 pounds, the amount of work performed in 100 hoppings would be about  $150 \times \frac{3}{4}$  (feet)  $\times 100$ , or 3750 foot-pounds. When the individual's weight is known, as it was in all of our cases, the approximate amount of work performed is easily computed. The weight of the individual was considered the only variant, as the height of hopping was controlled as much as it could be to about the average.

In our group of 124 normal cases the pulse-rate rose an average of 25 beats from the standing posture, as counted immediately after the exercise, or of 41 beats from the seated position. During the two minutes following the exercise it fell an average of 29 beats with the patient seated. There were no extreme variations in these figures, so that the results here obtained, and as shown in Fig. 1, may be taken as the normal pulse variations from the seated to the standing postures and also following the prescribed form and degree of exercise. We shall discuss the results in the groups of abnormal cases later.

**NORMAL EFFECT OF CHANGE OF POSTURE UPON THE BLOOD-PRESSURE.** The auscultatory method for blood-pressure examination should properly be applied with the patient's arm at the side of the chest, as the normal reading varies considerably with the arm in different positions. This holds for both the seated and the standing postures and even in the recumbent position, and was carefully adhered to in all our observations.

Change of posture causes a vasomotor effect that manifests itself by change of systolic and diastolic pressure and of pulse-pressure. This is the more marked the greater and the quicker the change of posture is executed. Crampton found that the systolic pressure is increased normally on change from the recumbent to the standing position, while in conditions of lowered vasomotor tone it remains the same or is decreased.

From the seated to the standing position the change is distinct and normally quite characteristic. In our group of normal cases the systolic pressure fell an average of 2 mm. of mercury on assuming the standing position. In the large majority of cases the change ranged



between a rise of 10 mm. or less and a fall of 10 mm. or less. In one case a rise of 26 and in two cases a fall of 24 mm. of mercury were the extremes.

The diastolic pressure rose an average of 7 mm. from the seated to the standing posture. It rose in almost every case, and in a few cases as high as 20 mm. of mercury; in a few cases it fell 10 mm.; in only one case did it fall 27 mm. The pulse-pressure fell an average

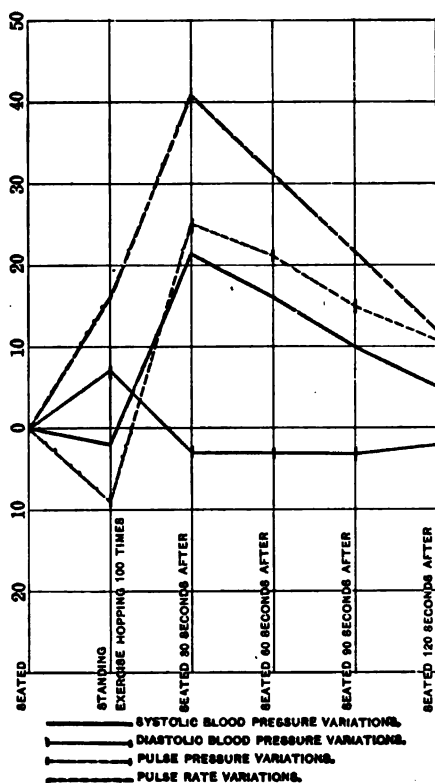


FIG. 1.—Results of functional tests made on 124 soldiers with clinically normal heart.

of 9 mm. of mercury on change from the seated to the standing position.

Blood-pressure studies were made in 7 normal cases of the effect of change from the recumbent to the seated position. The average results are shown in Table I.

TABLE I.

	Systolic.	Diastolic.
Recumbent position average . . . . .	101	55
Seated position average . . . . .	108	70
Average blood-pressure change . . . . .	+7	+15

**NORMAL EFFECT OF EXERCISE UPON THE BLOOD-PRESSURE.** Arno Lehdorff showed experimentally that stimulation of the splanchnics produces their contraction with increase of blood-pressure to a varying degree. This is also the normal effect of muscular work. Barringer described a test of heart function, using Graüpnér's method of making frequent readings of the pulse-rate and systolic pressure after measured amounts of work and clinically obtaining Lehdorff's results. If the heart's action becomes insufficient during exercise the blood-pressure falls. With recovery of the heart's contraction the blood-pressure rises again.

The "hopping exercise" was used in this study. The systolic pressure was measured thirty seconds after the completion of the exercise, with the patient seated; it had risen an average of 21 mm. of mercury in the group of normal cases from the previously seated position. The majority showed a rise of between 6 and 30 mm., the highest rise being 60 mm. in one case. In 3 cases only was there a fall of systolic pressure of 4, 5 and 9 mm. of mercury, respectively.

The diastolic pressure, thirty seconds after exercise, had fallen an average of 4 mm. of mercury from the previously seated posture. A slight fall of diastolic pressure was the usual finding, although a rise of 10 mm. or less occurred in a number of cases. In one case the diastolic pressure rose 25 mm. The pulse-pressure increased considerably with the exercise.

The systolic and diastolic pressures and the pulse-pressure gradually returned to almost the normal within about two minutes following the cessation of the exercise. Table IV presents the form in which our data were collected. Table II presents a list of characteristic readings, as they were calculated from the records of our normal group of cases.

TABLE II.

Normal change, seated to standing.			Normal change from seated, after exercise.									
Pulse-rate.	Systolic.	Diastolic.	Pulse-rate.		Systolic blood-pressure,				Diastolic blood-pressure,			
			Imme- diate.	Two min.	30 sec., -60, -90, -120.				30 sec., -60, -90, -120.			
+4	0	+4	+14	-12	+8	-2	-10	-6	+2	-4	0	+8
+18	0	-2	+24	-12	+41	-0	-22	-4	-8	+10	-4	+6
+16	-20	+12	+30	-24	+30	-14	0	-6	-2	0	0	+2
+22	-6	+10	+36	-36	+18	-2	-2	-10	-6	0	0	-2
+24	-8	+14	+42	-30	+6	-4	-18	-10	+8	0	0	+6
+24	-2	+9	+42	-48	+30	-4	-2	-2	+2	-10	+10	0
+18	-2	+2	+30	-24	+20	-18	-6	-6	-0	-2	0	0
+24	-18	-20	+26	-18	+24	-14	0	-6	-6	-6	-2	+3
+24	-14	+18	+44	-34	+46	-2	-6	-12	-6	-6	-2	-5
-8	+4	+14	+40	-42	+10	-6	0	-1	-4	0	-2	-8
+24	+10	+20	+20	-18	+34	-4	0	-4	-10	0	0	-2
+16	+10	+15	+52	-12	+8	-2	-10	-6	-2	-4	0	0
+12	-4	+18	+34	-46	+12	-4	-2	-6	+10	-10	0	0
+12	-6	-27	+28	-30	+18	-2	-14	-3	-6	+10	0	0
+18	-16	+22	+30	-26	+10	-4	-14	-12	+2	+12	0	+2

**FUNCTIONAL TESTS IN CASES OF SIMPLE TACHYCARDIA.** These observations were made upon a series of 32 cases. They all presented moderate tachycardia, above 100, and in most instances 120 beats a minute, more or less persistent, but without discernible cause and with otherwise normal hearts. The slight differences from the normal in the blood-pressure variations that this series exhibits are not striking enough to indicate specific value.

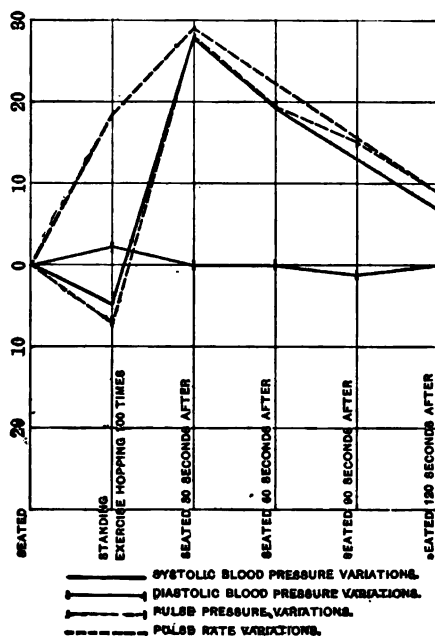


FIG. 2.—Results of functional tests made on 32 cases of simple tachycardia.

A comparison of Fig. 2 with the normal shows at a glance the one important feature revealed by functional tests in cases of simple tachycardia; that is, the effect of exercise upon the pulse-rate. The increase of pulse-rate in simple tachycardia as a result of exercise over the rate in the erect posture is much less than normal. The average increase after exercise was only 11 beats a minute; the variations above and below this were slight. The following table shows a characteristic series of the figures obtained:

TABLE III.

						Variation.
Pulse-rate seated . . .	120	128	102	120	108	°
Pulse-rate standing . . .	156	132	120	120	120	+18
Pulse-rate after exercise . .	144	132	144	156	132	+11
Pulse-rate two minutes after	132	126	126	126	120	-20

In 2 cases of sinus bradycardia, with persistent pulse of 60 and less, the results of comparative tests revealed what may be interpreted as vagotonic influence upon the pacemaker. Thus the pulse increased 25 from seated to standing, but exercise did not increase it at all, the effect being more complete than in simple tachycardia. The pulse then fell even lower than before. The systolic and diastolic pressure changes were quite normal.

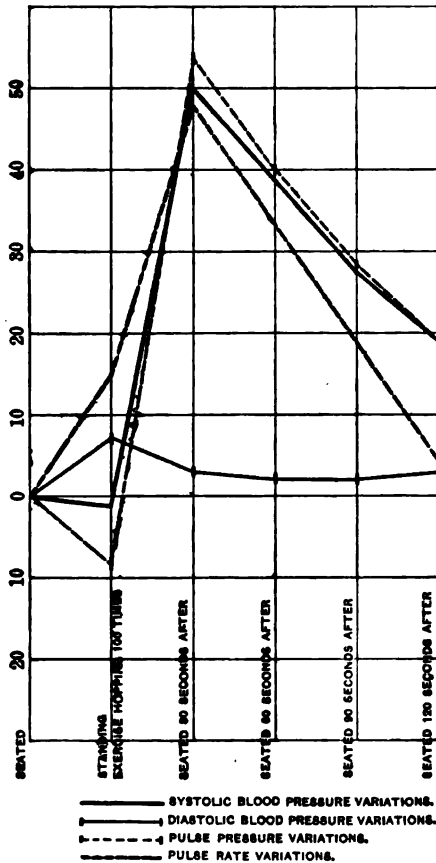


FIG. 3.—Results of functional tests in 5 cases of paroxysmal tachycardia.

**FUNCTIONAL TESTS IN PAROXYSMAL TACHYCARDIA.** Lewis pointed out a distinguishing feature between paroxysmal and simple tachycardia. He showed that effort has no effect on the pulse-rate during an attack of paroxysmal tachycardia while it increases the rate in other tachycardias. We have just shown that the increase of pulse-rate in simple tachycardia after exercise over the rate in the erect posture is much less than normal. Lewis's assertion was

not meant for the intervals between paroxysms. During these the pulse-rate increases a little more than in the normal cases both after change of posture and after exercise. This is shown in Fig. 3. Effort may induce a paroxysm, while, on the other hand, it is used by some patients to stop an attack.

The value of testing the functional capacity of the circulation in cases of paroxysmal tachycardia was emphasized in a previous study of the subject. Low arterial pressure is a constant finding in all these cases, though most marked during the attacks. The reason for this lies in the deficient filling of the ventricles during the very short diastolic periods. The period of ventricular systole is never more than 0.2 of a second. If the rate is over 200 per minute the period during which filling of the ventricles can take place is very short. As a result, venous stasis takes place and the arterial pressure falls.

From a study of the average pulse- and blood-pressure changes in our series of 5 cases, as diagrammatized in the figure, no characteristic findings can be attributed to this condition following the postural and exercise tests that we used in this study.

The following table presents the data as we collected them for analysis. Each double column is from a separate case:

TABLE IV.

	Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.
Pulse-rate, seated . . .	102	...	120	...	104	
Pulse-rate, standing . . .	120	...	144	...	120	
Blood-pressure, seated . . .	95	65	110	70	134	68
Blood-pressure, standing . . .	106	68	105	75	120	60
Exercise performed . . .	Hopping } one hundred times.					
Food-pounds of work . . .	3375	...	3750	...	...	3500
Pulse-rate immediately after . . . . .	162	...	120	...	144	
Blood-pressure 30 sec. after . . . . .	145	70	135	70	210	72
Blood-pressure 60 sec. after . . . . .	140	70	128	68	190	70
Blood-pressure 90 sec. after . . . . .	128	65	125	74	170	68
Blood-pressure 120 sec. after . . . . .	120	70	120	70	162	70
Pulse-rate 2 min. after . . . . .	114	...	114	...	104	

FUNCTIONAL TESTS IN THYROTOXIC TACHYCARDIA AND EXOPHTHALMIC GOITRE. Nine cases of exophthalmic goitre are here grouped together to ascertain the relationship of hyperthyroidism to the functional capacity of the circulation. The findings unequivocally support the belief that hyperthyroidism lessens markedly the cardiac and circulatory efficiency. This is evidenced by almost all of the tests used: The average increase of pulse-rate on changing from the seated to the standing posture is more than normal. Much more exaggerated than this, however, is the sudden tachycardia following exercise. In this series the pulse rose an average of 65

beats above what it was previously in the seated posture. The instability of pulse-rate in these cases is associated with an instability of blood-pressure. The fluctuation of diastolic pressure is quite marked. It rises with change of posture almost twice as much as it does normally and falls three times as much as normally following exercise. The diastolic pressure then remains low during the time of the test (Fig. 4).

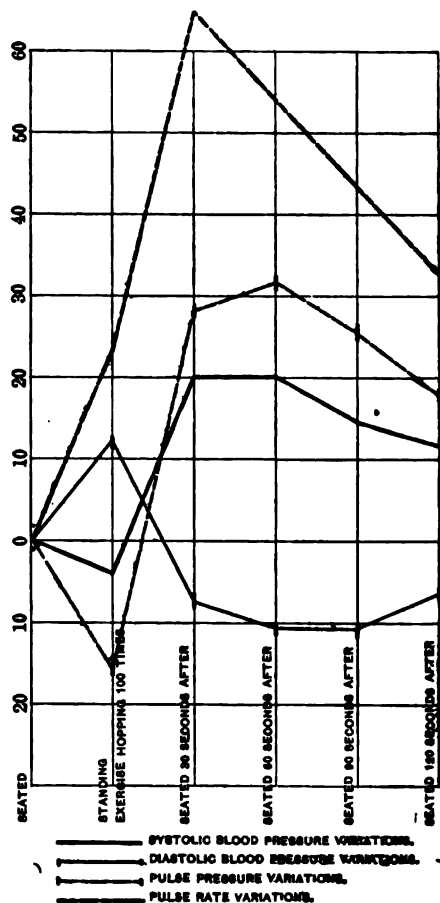


FIG. 4.—Combined result of functional tests made on 9 cases of exophthalmic goitre.

The systolic pressure shows a delayed rise following exercise in a few cases and gives the average of a sustained rise in the curve. This delayed rise or sustained level of blood-pressure signifies deficient circulatory efficiency. The pulse-pressure likewise shows a delayed increase, which is perhaps of equal significance. There were only slight variations from the average in the results of individual cases;

the curves constructed from readings in separate cases resemble the combined curve shown above. Thus, Figs. 5 and 6 are reproduced from the separate cases indicated in Table V.

TABLE V.

	Systolic.	Diastolic.	Systolic.	Diastolic.
Pulse-rate, seated . . . . .	68	...	112	
Pulse-rate, standing . . . . .	108	...	126	
Blood-pressure, seated . . . . .	136	90	145	84
Blood-pressure, standing . . . . .	134	106	142	74
Exercise performed . . . . .	Hopping one hundred times.			
Foot-pounds of work . . . . .	3375		4800	
Pulse-rate, immediately after . . . . .	156	...	192	
Blood-pressure 30 seconds after . . . . .	180	86	170	94
Blood-pressure 60 seconds after . . . . .	164	76	170	92
Blood-pressure 90 seconds after . . . . .	164	76	166	80
Blood-pressure 120 seconds after . . . . .	164	80	156	78
Pulse-rate 2 minutes after . . . . .	112	...	144	

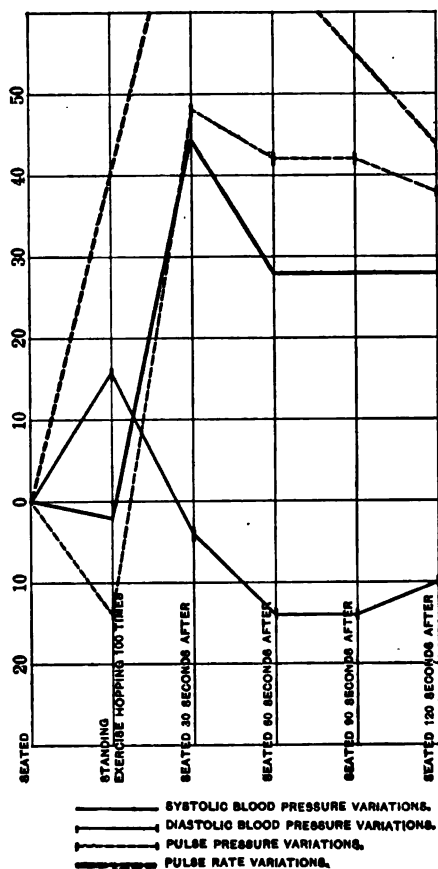


FIG. 5

Functional tests therefore confirm the attitude toward these cases that they are unfit subjects for strenuous work or prolonged exercise and strain.

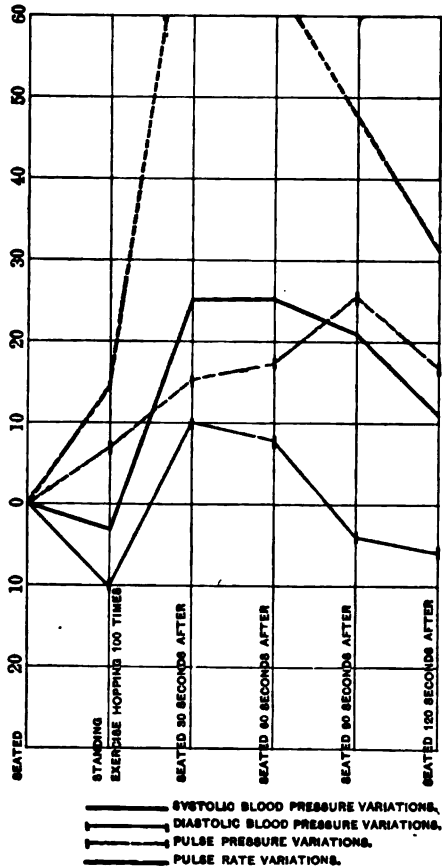


FIG. 6

**FUNCTIONAL TESTS IN NEUROCIRCULATORY ASTHENIA.** Neurocirculatory asthenia or the "effort syndrome" of symptoms is met with not alone in military life but also under the stress of civil and social relations. The disorder depends upon a vasomotor instability occurring in highly strung nervous individuals, and presents the following symptoms: breathlessness, precordial pain, a feeling of exhaustion, giddiness and fainting, palpitation, headache, lassitude, irritability, tachycardia, apical systolic thrill, high systolic blood-pressure and nervous instability. All these symptoms are exaggerated by effort and excitement.

In passing it may not be out of place to point out a differential point that has apparently not before been noted in the literature



between the thrill in this malady and that in organic mitral stenosis. The thrill in this disease, as also in some cases of thyrotoxic heart, is due to the diffusion of the apex-beat as it strikes over several rib spaces with a forcible or jerky movement. This systolic shock gives to the palpating hand the impression of a presystolic thrill. The thrill is recognized as a rumble characteristically when the chest-piece of the stethoscope covers a whole interspace, being applied over two ribs.

If now the stethoscope is placed obliquely upon the chest wall, so that its edge lies within an interspace and its mouth inclines toward either the upper or the lower rib, the rumble disappears. This is characteristic and almost always to be noted when there is a thrill in these cases. In mitral stenosis, however, the distinct presystolic wave persists against any adventitious attempts to obliterate it. The cardiogram in mitral stenosis is also different from that of this condition (Fig. 7 *a* and *b*).

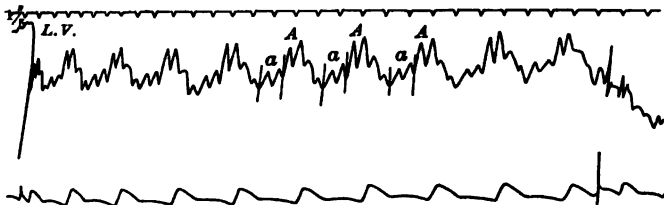


FIG. 7a.—Cardiogram from a case of mitral stenosis.

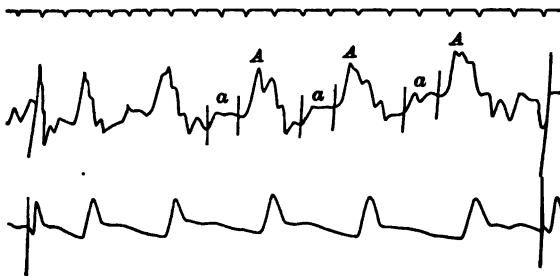


FIG. 7b.—Cardiogram from a case of neurocirculatory asthenia.

The one important feature that dominates the cardiac signs of this malady is the hypertonicity of the heart muscle. This can be recognized on palpation and auscultation and is exaggerated by exercise. The hypertonic condition and action of the heart muscle depend upon the hypertensive nervous state that is responsible for most of the other symptoms. Tests for increased tonicity of the heart muscle have not as yet been developed, and we must therefore rely upon our clinical acumen and experience to recognize and estimate it.

McNee and Dunn, and more recently Brooks, found the thyroid gland enlarged in many of these cases and consider the condition thyrotoxic. We believe that the clinical picture is neurogenic and psychogenic primarily rather than induced by endocrinal disturbance. Neurocirculatory asthenia presents a tremogram different from that obtained in hyperthyroidism. The thyrotoxic tremor is fine and at a fairly regular rate of about eight to the second, as shown in Fig. 8. The tremogram of neurocirculatory asthenia is rather coarse and irregular and the irregularity increases in rate and amplitude upon effort (Fig. 9). The tracings were made by using the tambour of the Mackenzie polygraph attached to the tip of the middle finger of the outstretched hand with the forearm supported.

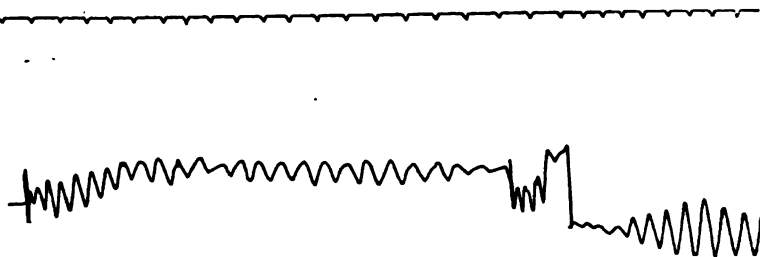


FIG. 8.—Thyrotoxic tremor.

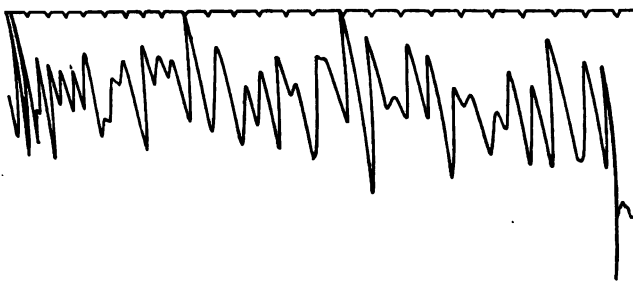


FIG. 9.—Tremogram from a case of neurocirculatory asthenia.

The curve that we have constructed from studies made upon 28 cases of neurocirculatory disorder which presented the classical symptoms shows: (1) increase of pulse-rate on change of posture and following exercise greater than normal; (2) fall after exercise more gradual than normal; (3) increase of systolic blood-pressure and of pulse-pressure more than in the normal cases immediately after exercise.

It must be emphasized, however, that the hypertonic state of the heart muscle as a feature of this disease is of equal importance with the exaggeration of the symptoms and signs by effort or excitement.

With regard to the pulse-rate, what is probably more character-

istic than its exaggeration after exercise and its more gradual return than normally is the instability of rate due to psychic factors (Fig. 10).

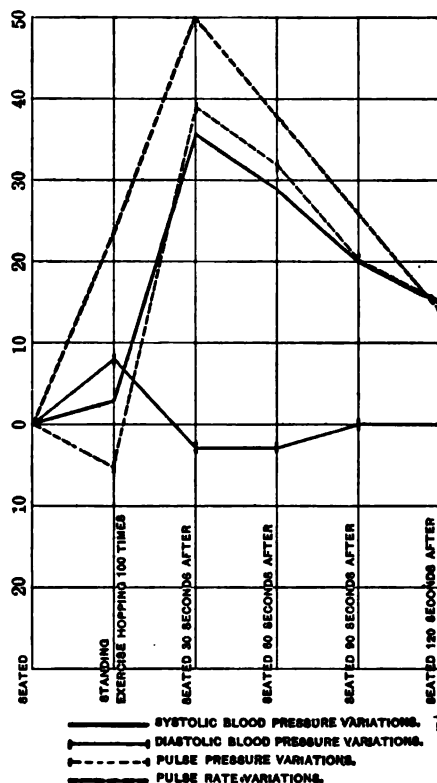


FIG. 10.—Result of functional tests made on 28 cases of neurocirculatory asthenia.

Table VI shows characteristic figures from our protocols of cases of neurocirculatory asthenia. Each double column is from a separate case.

TABLE VI.

	Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.
Pulse-rate, seated . . . . .	84	...	96	...	90	...	114	...	96	
Pulse-rate standing . . . . .	132	...	132	...	132	...	132	...	108	
Blood-pressure, seated . . . . .	115	75	130	64	108	68	120	70	122	70
Blood-pressure, standing . . . . .	145	90	138	84	120	86	115	75	128	84
Exercise performed . . . . .	Hopping one hundred times on one foot.									
Foot-pounds of work . . . . .	3425	...	4250	...	4685	...	3375	...	3225	
Pulse immediately after . . . . .	156	...	144	...	156	...	192	...	120	
Blood-pressure 30 seconds after . . . . .	145	80	144	76	154	72	160	70	156	90
Blood-pressure 60 seconds after . . . . .	140	80	144	76	144	68	160	65	136	80
Blood-pressure 90 seconds after . . . . .	120	85	142	72	138	66	150	65	140	84
Blood-pressure 120 seconds after . . . . .	135	80	140	68	134	64	134	70	124	76
Pulse 2 minutes after . . . . .	120	...	78	...	132	...	132	...	108	

It is apparent from the curves and from the table that patients with the effort syndrome may have normal cardiac reserve power. There is no delayed rise of the systolic blood-pressure after the exercise. This accords with the findings in 3 cases examined by Robey and Boas.

Tests were made in 3 cases of neurocirculatory asthenia of the effect of change from the lying to the seated position and from the lying to the standing position. The changes depend upon splanchnic effects. (Table VII.)

TABLE VII.

	Systolic.	Diastolic.
Recumbent position—average . . . . .	127	65
Seated position—average . . . . .	132	79
Average variations . . . . .	+5	+14
Recumbent position—average . . . . .	126	64
Standing position—average . . . . .	124-134	60-73
Average variation . . . . .	-2 +8	-4 +9

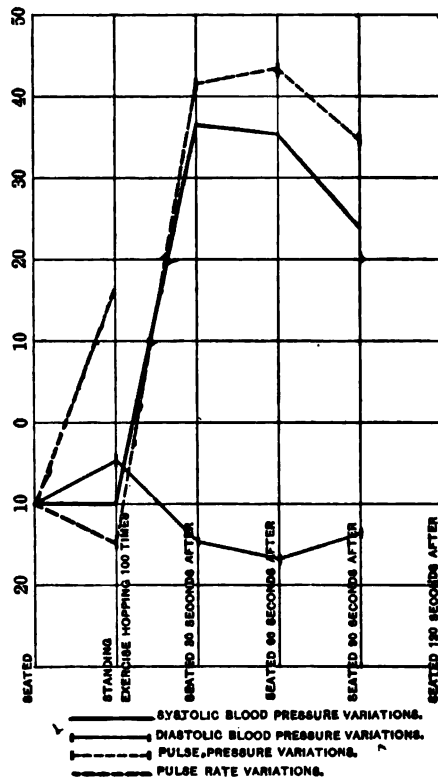


FIG. 11.—Blood-pressure studies on 11 cases of nephritic hypertension.

Sudden change from the recumbent to the standing position causes a slight fall of blood-pressure. But after about fifteen seconds, both the systolic and diastolic pressures rise as in the normal cases.

**FUNCTIONAL TESTS IN NEPHRITIC HYPERTENSION.** We studied 11 cases of hypertension of nephritic origin and desire to note what general effect hypertension alone may have upon the functional capacity of the circulation. The lowest diastolic pressure in our series was 90 mm. of mercury. The pulse-rate was augmented more than normally by change from the seated to the erect posture. It is to be regretted that our data of pulse-rate following exercise are too incomplete to warrant any conclusions regarding it. The diastolic pressure rose on standing and fell after exercise, giving a curve very much like the normal (Fig. 11). The systolic pressure was uninfluenced

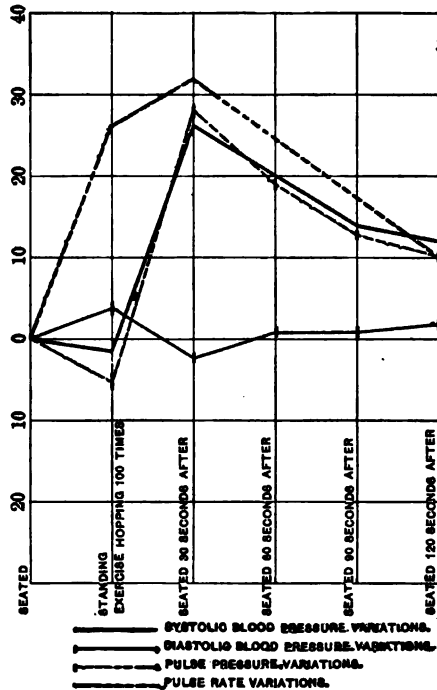


FIG. 12.—Combined results of functional tests in 12 cases of mitral regurgitation.

by change of posture from seated to standing. Exercise increased the systolic pressure almost twice as much as normally, and, what is more important, the Barringer test, *i. e.*, the systolic pressure taken thirty, sixty and ninety seconds after exercise, indicates, if not a delayed rise, an increased pressure maintained longer than normal. The pulse-pressure does show a distinct delayed rise. That is, cases of nephritic hypertension, as concluded from our evidence, have a diminished functional capacity of the circulation. Because of the distress after exertion we were prompted to caution in these cases and no more strenuous exercises were used for our observations.

**FUNCTIONAL TESTS IN MITRAL REGURGITATION** (Fig. 12). In 12 cases of fully compensated mitral regurgitation the blood-pressure

reactions were normal. The changes of pulse-rate were almost exactly like those in our group of cases of simple tachycardia. That is, change of posture from seated to standing increased the rate more than normally; exercise, however, effected the same change as appeared so characteristically in the cases of simple tachycardia and even more marked, *i. e.*, only slight increase of pulse-rate, an average of 6 beats per minute. The construction to be put upon this finding is problematic. It is possible that some infectious process was at work in the cases of simple tachycardia that would later have produced auscultatory signs of valvular change.

**FUNCTIONAL TESTS IN AORTIC REGURGITATION.** Aortic regurgitation presents characteristic blood-pressure curves. The combined results obtained from 5 cases are strikingly pictured in Fig. 13.

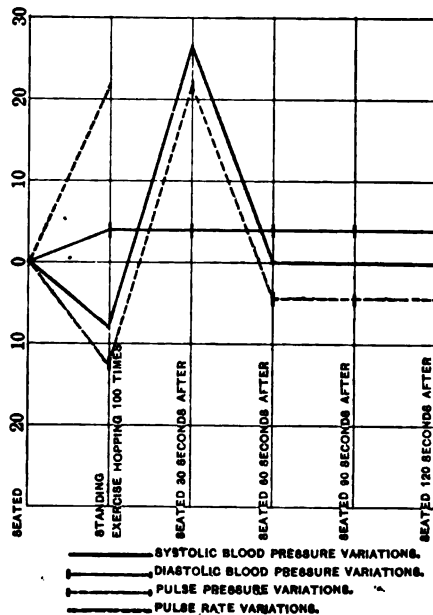


FIG. 13.—Representing the combined functional tests in 5 cases of aortic regurgitation.

The systolic pressure falls much more than normally on assuming the erect posture. This probably depends upon the change in hydrostatic pressure of the column of blood, and, as Hill pointed out, is exaggerated in aortic regurgitation. With exercise the systolic and pulse-pressure rise more than normally; what is interesting and striking is the sudden fall of systolic and pulse-pressure back to normal within one minute after the exercise.

**FUNCTIONAL TESTS IN CONGENITAL LESIONS AND CARDIAC DISPLACEMENT.** These tests were not done extensively enough to warrant detailed analysis. The findings may be briefly summarized.

In 1 case of congenital dextrocardia with transposition of the viscera, findings were obtained quite different from the normal. The main feature was a marked fall, 14 mm. of mercury, in the diastolic pressure on change of position from sitting to standing and its return to 5 mm. above the previous reading after exercise.

The same feature singularly characterized a case of patent ductus arteriosus. A fall of diastolic pressure of 30 mm. occurred in this case and persisted after exercise. It is hoped that the effect of congenital heart lesions upon functional efficiency will be given further study.

In the 2 cases of markedly displaced heart, very peculiar findings were obtained, chiefly an instability of pulse-rate variations. The findings are not sufficiently convincing or numerous to report in detail. The results in the case of auricular flutter were noted in a previous study.

**SUMMARY.** 1. Comparative functional tests of the circulation were made in 233 cases, including the normal, the various tachycardias, sinus bradycardia, thyrotoxic conditions, neurocirculatory asthenia, etc.

2. The normal changes of pulse-rate and blood-pressure are presented in detail and are used as standards for comparison both graphically and in the individual analyses.

3. The characteristic finding in simple tachycardia, in compensated mitral regurgitation and in sinus bradycardia, was the absence of any effect upon or only very slight increase of the pulse-rate after exercise.

4. In thyrotoxic heart the characteristic effects were marked instability of the pulse-rate, with great increase after exercise, associated with an instability of the diastolic blood-pressure.

5. A similar effect, but less marked, was found in neurocirculatory asthenia. In the latter condition it is noted that the thrill disappears when the relationship of apex-beat to chest wall is disturbed or distorted on auscultation. The tremogram is recorded as a differential point between neurocirculatory asthenia and thyrotoxic conditions.

6. Hypertonicity of the heart muscle is the physiological basis of the cardiac signs in neurocirculatory asthenia.

7. Thyrotoxic conditions and nephritic hypertension lessen the functional circulatory capacity.

8. Aortic regurgitation and congenital heart lesions gave fairly distinct features, but further studies along the lines indicated are suggested to establish the results in congenital heart.

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### LEFT APICAL IMPAIRMENT IN MITRAL STENOSIS.

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In a fairly large proportion of cases of mitral stenosis there may be obtained a history of hemoptysis. In certain cases this may be the first symptom of any physical defect, and it is because of this spitting of blood, cough, shortness of breath and some weakness that the patient first seeks medical advice. The history being suggestive of tuberculosis, and there being present on examination certain physical signs further suggestive of this condition, the diagnosis is many times confused unless a careful examination of the heart is made at the same time. The presence of impairment of resonance over the left apex anteriorly may be so striking that the lung is wrongly held to be the source of the symptoms, and without seeking further the case is diagnosed as pulmonary when the trouble may be distinctly cardiac. The association of pulmonary signs in mitral stenosis has been a matter of great interest to one of us (G.) for a number of years, and because so little attention has been directed to it in medical literature, we have devoted considerable study to this question while pursuing our work as heads of the special boards for cardiovascular and tuberculosis examinations respectively at Camp Jackson.

The diagnosis of mitral stenosis is oftentimes obscure and difficult, and many times it is overlooked because at hasty examination the



outstanding characteristics of a presystolic murmur and presystolic thrill have not been pronounced. As pointed out by one of us (G.) in a previous paper in this JOURNAL, the following findings establish a diagnosis: Snappy quality of the first sound and systolic tap or shock on palpation, absence of hypertrophy of the left ventricle in the cases uncomplicated with insufficiency, presystolic thrill, presystolic murmur and accentuation of the second pulmonic sound.

The history of rheumatic fever, chorea, tonsillitis and growing pains when authentic is an added evidence, but army histories can be depended upon to no such extent as in civil life. Examination for the above features should be made with great care, with the patient erect, recumbent (not omitting the examination with the patient lying on the abdomen) and before and after exercise test. Murmurs may be missed when the patient is erect and with the heart at rest, and may be very clearly heard when recumbent and with the heart beating more forcefully; as after exertion.

Cases of suspected stenosis as they presented themselves in the draft were studied in this way, and following the heart examination were thoroughly studied from the standpoint of the lungs. In a few instances, in addition to the physical examination, roentgen-ray studies were made, but this aid was not uniformly sought, as the Base Hospital was at some distance from the field of activity of the examining boards and but little time was allowed us to study rejected cases, as they were returned to their homes as soon as they were found to be unfit for general military duty. As controls, many normal cases were studied with respect to the left apical dullness, and all types of individuals, without reference to their physical development, were included.

The cases which we have studied together are summarized below. To avoid repetition it may be stated that the diagnosis of stenosis was definite:

CASE I.—Left chest noticeably flat, with less muscle tissue. Dull in both infraclavicular fossæ, left very slight. Inspiration over the left apex harsh, but no other change.

CASE II.—Dullness about the third left rib to the clavicle, extending from the left border of the sternum to slightly within the left midclavicular line. No change in breathing; respiratory sounds faint over the entire chest. No change in voice sounds or fremitus. Krönig's isthmus (KI) not contracted. Slight lessening of resonance above the clavicles, but not dull. No change posteriorly. Indeterminate rales heard over the right lung, due to diffuse bronchitis.

CASE III.—Dullness moderate above the second space to the clavicle on the left side; extends outward to MCL from the left border of the sternum. No voice or breath changes. Dullness above the right second rib. No change posteriorly. No rales and no contraction of KI.

**CASE IV.**—Moderate depression of supraclavicular fossæ. KI not contracted. Dulness in right first interspace and over the left infraclavicular region from the lower border of the second rib to the clavicle and from the sternum to beyond MCL. Both voice and breath sounds normal, but exaggerated over both lungs.



**CASE V.**—Dulness above the second right rib; above the third left rib dulness from the sternum three-quarters of the way to MCL in the second interspace and to MCB in the first space. Higher pitch on the right of the sternum. KI normal.

**CASE VI.**—Dulness over both infraclavicular fossæ, right evident near the sternum. On the left side dulness to beyond MCL and extending below the second rib, giving an impression of a distinctly large dull area. Otherwise negative.

**CASE VII.**—Dulness over both infraclavicular regions. On the right side it is well within MCL, close to the sternum, and not below the second rib. On the left side it is well beyond MCL and below the second rib. The note is distinctly higher pitched than on the right side, and it is evident that the area of dulness is larger on this side than on the right. Voice sounds are negative, but the breath sounds are somewhat bronchovesicular. KI normal.

**CASE VIII.**—Dulness above the right second rib, also in the left infraclavicular fossa to the third rib, blending with heart dulness and extending outward to MCL. Left apex above clavicle not dull. KI normal. Right apical dulness similar to that on the left side, but KI is narrowed. Otherwise negative.

CASE IX.—Dulness in both infraclavicular fossæ, the larger area being on the left side, extending beyond MCL. Voice and breath sounds negative, except over the area 1 cm. in the diameter in the second left space, where the voice transmission is marked. Otherwise negative.

CASE X.—Dulness above both the second ribs, much higher pitched on the left than on the right side. KI normal. Otherwise negative.

CASE XI.—Dulness above both the second ribs. Very little difference in pitch between the two sides. Dulness extends through both MCL, with diminishing resonance toward the limits of the area. (Subject very muscular and well nourished.) KI normal. Otherwise negative.

CASE XII.—Dulness in both infraclavicular fossæ, the left higher pitched and more extended than on the right, extending well beyond MCL. Below the left second rib there is diminished resonance, more marked than on the right side, but not dull. Right KI less than the left. Otherwise negative.

CASE XIII.—Right apex somewhat contracted. Dulness in first interspace on the right and left sides. Markedly higher pitch on the left than on the right side, also dulness in the left supraclavicular fossa. Voice transmission increased above the third left rib and above the eighth dorsal vertebræ on the right. KI normal. Otherwise negative.

CASE XIV.—Dulness over both infraclavicular fossæ; on the left it is more extensive than on the right. Breathing higher pitched at both apices and harsher over the left upper lobe on inspiration than on the right. KI normal. Otherwise negative.

CASE XV.—Chest somewhat flat. Dulness over both infraclavicular fossæ, but left is higher pitched. No difference in extent. Slight prolongation of expiration on the left. Expiration not high pitched. KI normal. Otherwise negative.

CASE XVI.—Right supraclavicular fossa depressed. Dulness on the right side anteriorly above the fourth rib. On the left side dulness above the third rib, well within MCL. Diminished breathing over the right upper lobe, with increased vocal resonance. Bronchovesicular breathing over the left upper lobe, with prolonged high-pitched expiration. Roentgen rays show a patch of infiltration in right infraclavicular fossa.

CASE XVII.—Dulness over the right side above the right third rib; on the left side, above the second rib. Both supraclavicular fossæ somewhat dull. KI diminished on both sides. Poor respiratory sounds, but otherwise negative.

CASE XVIII.—Moderate retraction of both apices, moderate narrowing of KI. Moderate dulness over both apices to the fourth rib on the right side and to the third rib on the left. Dulness is marked above the second left rib outward to MCL. Diminished

breath sounds over both lungs, with expiration somewhat prolonged and high pitched at the left upper. Otherwise negative.

CASE XIX.—Dulness in both infraclavicular fossæ—left higher pitched and of wider extent, extending from sternum to MCL and downward slightly below the second rib. KI normal. Otherwise negative.

CASE XX.—Dulness on both sides of the sternum in the infraclavicular fossa. The left is higher pitched, extending below the second rib and outward to within MCL. KI normal. Otherwise negative.

CASE XXI.—Slight depression of both supraclavicular fossæ, left more marked. Both KI somewhat diminished. Dulness above the right and left second ribs. On the left side from the sternum to one-third length of the clavicle the note is somewhat higher pitched than on the right side. Breathing diminished over both lungs. Otherwise normal.

CASE XXII.—Impaired resonance from the left second interspace (middle) upward to a finger's breadth above the clavicle and extending laterally to MCL. Posteriorly, dulness is found from the third dorsal spine upward for 3 cm. Breath sounds increased as compared with the right side and expiration is prolonged. KI normal. Roentgen rays show numerous small areas of infiltration throughout both lungs, being more marked in the right upper lobe.

CASE XXIII.—Apices not retracted. Dulness above the second rib on the right side, also on the left and more marked on the left side, extending beyond MCL. Breathing normal on the right, expiration prolonged on the left, not higher pitched or harsher except above the left second space. Otherwise negative.

CASE XXIV.—Vocal fremitus increased over the left upper lobe and slight dulness from the upper border of the third left rib to the clavicle, extending outward to within MCL. Prolonged expiration over the left upper lobe and marked harsh breathing on the right. Roentgen rays show evidence of old tuberculous lesions.

CASE XXV.—Supraclavicular fossæ not retracted. Dulness present in the right and the left second spaces to the clavicle, being more marked near the sternum, but extending on the left side to MCL and beyond. Somewhat harsher breathing above the second left rib. Otherwise negative.

CASE XXVI.—Dulness of the left infraclavicular fossa to the second interspace and one-half of the distance to MCL. Otherwise the examination is negative.

CASE XXVII.—Dulness on the left side extending to the outer border of the clavicle and as low as the third rib, being more marked beyond MCL. Dulness more marked than on the right side. Otherwise negative. The illustration is from this case and shows the characteristic impairment of the left apex in a classical case of mitral stenosis. The extent of the dulness and the intensity as compared with the normal right apex is shown.

It is important to bear in mind that the left apical dulness occurs

with persistent regularity in mitral stenosis and is not met with in other cardiac disorders. Emphasis is laid on this fact because it is not infrequently the case that hemoptysis and shortness of breath, with other signs of failing health, are early symptoms in mitral stenosis. The similarity between pulmonary tuberculosis and these cases of stenosis, so far as symptomatology is concerned, is striking, and unless one is alive to the fact that mitral stenosis may be at the bottom of the trouble, one is apt to be misled by the existence of a well-marked left-sided apical dulness.

The dulness which we believe to be characteristic of mitral stenosis is found generally anteriorly above the third rib, extending to the clavicle and in some instances above it. It extends a variable distance to the left, at times as far as the outer third of the clavicle. It is unassociated with rales, as a rule, and the voice sounds are not characteristic, while the breath sounds assume a bronchovesicular quality at times. The cause of the dulness or impairment we believe to be an enlargement of the left auricle, which in some cases mutes the sound waves elicited on percussion by its contact with the lung and in other cases causes actual compression of the lung itself. In as much as the dulness is found in the cases in which no Graham-Steell murmur is heard, dilatation of the pulmonary artery probably plays an insignificant role in the production of the dulness.

In cases in which left apical dulness is encountered, we recommend that a diagnosis of tuberculosis be withheld until the heart has been carefully examined for the possible existence of mitral stenosis.

### **A BIOLOGICAL CONCEPTION OF NEOPLASIA, ITS TERMINOLOGY AND CLINICAL SIGNIFICANCE.\***

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THE efficiency of the medical profession is dependent upon at least four things, *i. e.*, perfection of its conceptions, perfection of methods, accuracy of investigation and a large amount of kinetic energy. One of the most important economic subjects which have occupied the attention of the profession and demanded perfect conceptions is that of neoplasms.

I shall not review in detail the facts<sup>18</sup> which have led to the apparently radical declaration that the conception or conceptions which the medical profession possesses of the biogenesis, histogenesis, morphology, terminology, classification and clinical behavior of neoplasms are based upon a few facts and a great amount of speculation and empiricism.

\* Presented before the Meeting of the Washington, Oregon and Idaho Tri-Stat Medical Association, Seattle, Washington, 1918.

From a biogenetic standpoint, the profession has been willing to assume the "rest hypotheses" of Cohnheim,<sup>5</sup> Ribbert,<sup>28</sup> and their followers, for which there has been no absolute anatomic or experimental proof.<sup>4 13</sup> From a histogenetic standpoint it has been assumed that neoplastic tissues represent an abnormal state or condition of normal tissues<sup>29</sup> and therefore take their origin from the arbitrary three-layer stage of embryonic development,<sup>30</sup> a basis for a conception which modern biologists agree has many contradictions in nature, especially when applied to tissue regeneration,<sup>26</sup> of which neoplasia is but a non-communistic phase.<sup>16</sup>

Morphologically, the cells of neoplasms of the different layers of the three-layer stage are frequently indistinguishable.<sup>19</sup> Our terminology applied to neoplasms is a mixture of ancient gross descriptions, comparison to unrelated things, and names of normal tissues. Our classifications have been made upon a histogenetic basis with which a recent excellent authority (Mac Callum<sup>14</sup>) has demonstrated his dissatisfaction by declaring that classification is not possible; he contents himself merely with an "arrangement" of neoplasms.

Before attempting to establish a basis for a biological conception of neoplasms it may be well to review the opinions of some of the leading teachers of pathology. The following quotations are either direct, in the language of the authors, or literal translations:

"One can arrange tumors according to their structure and their genesis into three groups, *i. e.*, connective-tissue tumors, epithelial tumors, teratoid tumors and cysts. It must be mentioned, however, that many tumors allow themselves to be grouped in two or even three groups." (Ziegler.<sup>31</sup>)

"The classification of tumors has been made in different ways. It seems best to me to arrange them according to their histogenesis as most authorities have done. There is, however, the difficulty that many new-growths develop from the same tissue, thereby making the number of new-growths greater than the number of normal tissues. Therefore a histological classification according to tissue relationship also recommends itself." (Ribbert.<sup>28</sup>)

"At the beginning of this chapter certain broad lines of classification that have been adopted in the case of new-growths were discussed, and it then was said that the best method of classification is one which depends upon an anatomical basis subject to the great distinction of neoplasms into non-malignant and malignant. If, then, we take the two great divisions, non-malignant and malignant, and subdivide these severally into epithelial and connective-tissue groups, we shall be able to account, in one or other of them, for the great majority of tumors. It will prove of assistance, however, if at the same time we pay some attention to the classification based upon embryological data." (Lazarus-Barlow.<sup>12</sup>)

"It is not possible today to make a satisfactory scientific classi-

fication of tumors; but the fact that they are composed of structures which resemble the various morphological types of tissues found in the normal body suggests a grouping of the various forms which may be regarded as a useful and suggestive catalogue. It should be remembered that the usual separation of the normal tissues into groups is useful, rather because it facilitates their study than because it expresses absolute and fundamental distinctions; and the same may be said of all the classifications of tumors. An increase of our knowledge concerning their structure and genesis will doubtless lead to a more accurate grouping of tumors; but for the present such an arrangement as that indicated below\* will be found of practical value for the progress of study. The attempt has often been made to classify tumors with reference to the developmental history of the tissues represented and it has been generally believed that cells once differentiated in the primary embryonic layers cannot again be merged in type. While this principle holds good in general, especially for highly differentiated forms, certain recent studies have seemed to indicate that even this distinction may not be inflexible. However this may be, it is certain that the cells derived from one embryonic layer may, under special conditions, come so closely to resemble in morphology those of another layer, that a structural differentiation, with our present resources at least, is not always possible. While, therefore, this which is called the histogenetic principle of classification is most suggestive and may be useful in connection with other data in the study of tumors, it seems to the writers that it is wiser for the present not to base our classifications too largely upon embryological data in several particulars still subject to controversy." (Delafield and Prudden.<sup>9</sup>)

"The imperfect state of our information concerning the ultimate cause of the various forms of tumors makes the matter of classification difficult; and while numerous systems have been proposed the test of increasing knowledge has shown weak points in them all. It must not be forgotten, however, that the present classification and terminology are largely artificial, and that insensible gradations occur which unite the varieties of tumors so as to leave no definite line of separation. Since the time of Virchow's classic production a vast amount of information upon tumors in their various aspects has been recorded and to this fund of knowledge each passing year makes its contributions. Paradoxical as it may seem, however, our increasing knowledge has in certain directions *only served* to make more confusion, and in one particular direction, *viz., as regards the cause of tumors in general*, speculation is as rife and almost as fruitless as it was before the modern era. Without a clear conception of all the factors which lie at the beginning of tumor formation it is

\* This refers to the classification of the authors quoted. The classification may be found in their text-book of pathology.

not possible sharply to define them. How difficult the matter of definition is can best be illustrated by noting the fact that almost every prominent authority upon tumors has given a definition differing from that of others working in the same direction." (Hektoen-Riesman.<sup>11</sup>)

"The question is: Can the histogenetic conception, in spite of the uncertainty of observations, be used as the principle of classification of tumors? Yes. At this time a combined morphological and histogenetic conception for the classification of tumors recommends itself to me. However, one must also take biological relations into consideration." (Borst.<sup>3</sup>)

"So great is the diversity of structure in tumors, so uncertain, in many cases, is the histogenesis, that a classification based as is the classification of the normal tissues, on structure and histogenesis presents great difficulties." (Councilman.<sup>7</sup>)

"Tumors are classified, like normal tissues, on a histological basis; that is, on the differentiation of the cells composing them. When the differentiation of the cells is marked, as it ordinarily is in slow-growing tumors, a diagnosis of the nature of the tumor is usually easy. When the growth is rapid, however, the differentiation is slight and may be entirely wanting. In the latter case we may be able only to guess at the probable diagnosis from the situation in which the tumor grows, or from having for comparison with it a series of tumors of the same nature growing at all rates of speed. Sometimes, too, in a part of the tumor the cells may grow slowly so that more or less differentiation of them has had time to take place and from them the character of the growth can be ascertained. The nomenclature of tumors is very unsatisfactory. Most names were applied long ago when much less was known about tumors than now. Consequently they may have become heirlooms which are not easily cast off. Many improvements in names have been suggested and a few have been generally accepted." (Mallory.<sup>20</sup>)

"Too often have theories as to the causation of those autonomous neoplasms entered into the definitions. Thus, Cohnheim defined them as 'circumscribed atypical productions of tissue from a matrix of superabundant or erratic deposit of embryonic elements.' Here we have introduced the untenable theory that all autonomous neoplasms arise from embryonic tissue which has remained latent. We are still uncertain as to the causation of these growths, and so etiology must not enter into our definition. Thus, Ziegler's definition is more satisfactory, 'a tumor is a new formation of tissue possessing an atypical structure, not exercising any function of service to the body, and presenting no typical limit of growth.' The use and limitations of the term 'atypical structure' require here a little explanation, add to which, the pure teratomas to be presently described do present a limit of growth; and so we prefer C. P. White's statement that 'a tumor proper is a mass of cells,



tissues, or organs, resembling those normally present, but arranged atypically. It grows at the expense of the organism without at the same time subserving any useful function.' Von Rindfleisch characterizes them as a 'localized degenerated excess of growth;' *i. e.*, the very excess of growth is regarded as in itself a degeneration; Birch-Hirschfeld, as originating spontaneously, becoming separate from the physiological tissues in their physiological and functional relationships, as developing from the cells of the body, and possessing progressive growth; Ribbert, as 'self-confined, dependent upon the organism for their nourishment, but otherwise largely, if not quite independent, corresponding more or less but never absolutely with the tissues of the natural body, and presenting no definite limit to their growth.' Lubarsch's definition is closely allied: 'Under tumor proper we have to understand those growths of apparently independent origin which histologically correspond in structure more or less completely with the matrix from which they originate, but in form are atypical; which further, in spite of their organic connection with the matrix, and in subjection, apparently, to laws of their own, pursue an independent existence which is not, or only exceptionally, of advantage to the organism as a whole.' " (Adami.<sup>1</sup>)

The last authoritative writer (MacCallum) in text-book form upon the subject of neoplasms is perhaps the most conservative. He expresses a certain conciliatory attitude with the insufficiency of scientific knowledge and clearly generalizes in a manner which will be productive of future progress. "Rather than assume too accurate a knowledge of the ultimate derivation of the tumors, I have preferred to arrange them according to the general character of their tissues, both anatomical and biological, and their form. The following list is mainly for convenience in summarizing the various forms as they have been considered here. It is an arrangement, not a classification." (MacCallum.<sup>14</sup>)\*

These quotations, representing the best opinions upon the status of the conception of neoplasms, may be supplemented by the following list of expressions which have been utilized in the literature relating to neoplasms.

Thus authorities have stated that neoplasms represent: A specific tumor diathesis; a nutritional disturbance of the equilibrium of vegetative and functional cell power; a change between the relation of nerves to cells; a reduction of the avidity of the body cell; a primary emancipation of cell-growth from the normal laws of growth; a cellular atavism; a return to the embryonic condition of cells; an inherited or acquired intracellular abnormal metabolism; a cessation of the regulating growth influence of cell differentiation; an inherited pathologic quality of cells; a failure of cells to differen-

\* His list of tumors need not be published here because those who are interested in the details which have led up to these generalizations will of necessity examine the subject more thoroughly.

tiate; a disturbance of the idioplastic formation of cells; the formation of a "new race of cells," a prenatal separation of cells; a postnatal separation of cells; a primary inherited change in the nature of cells; a change in the biological behavior of cells; a product of connective-tissue senility; an heteroplastic change of the fixed connective-tissue cells; a congenital anlage; a release of the organic connection of cells; a separation of germinal cells; an embryonic separation of cells; a shunting of germ cells from their normal relations without misplacement; superfluity in the development of cells or tissues; separated germ cells; misplacement of cells; an abnormal persistence of embryonic cells.<sup>6</sup>

The multiplicity of diverse explanations, in itself, indicates dissatisfaction with the lack of accurate or scientific knowledge which we possess relative to the condition.

In the midst of such chaos one great and dominant generalization stands out. It is uppermost in practically all minds of the medical profession in all lands and forms the main basis of opposition to any new conception, which is in any way contradictory to it, *i. e.*, in 1877 Cohnheim<sup>6</sup> said, in his *Vorlesungen über Allgemeine Pathologie*, "I believe that this process, referring to the embryonic development of the *monstra per excessum*, such as superfluous fingers, giant children, giant adults, giant extremities, etc., is not only confined to this field but also applies to a much wider and more important field, namely, the field of true neoplasms."

In these words we find a generalization from a speculative correlation of some facts in the form of an hypothesis put forth by a great teacher for the inspiration of his students. Such hypotheses, although they may be proved later to be incorrect, are certainly means of correlation for future observations. In fact, it was a search for some justification for the hypothesis of Cohnheim which led to the following observations and generalizations.

Before proceeding to a presentation of the facts which form the basis of a biological conception of neoplasms it may be well to answer the question: What should constitute a perfect conception of neoplasms?

1. We should know the cells from which neoplasms develop since every living thing evolves from something living.

2. We should know what occurs to make some of the cells of neoplasms resemble normal tissues.

3. We should know the morphology of the component units of neoplasms.

4. We should have, if possible, a definite descriptive terminology which possesses biologic, histologic, and morphologic significance.

5. We should have a classification based upon biologic, histologic and morphologic facts and their clinical significance for economic purposes.

6. We should be able to prognosticate the clinical behavior of

neoplasms or at least know definitely *why* we cannot accurately prognosticate, since negative knowledge is *often* as valuable as positive knowledge.

7. We should know both the biologic and specific causes for the development of neoplasms.

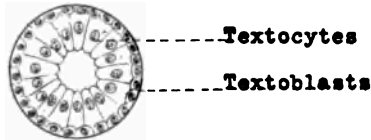
In 1909 the writer<sup>18 20</sup> undertook an investigation of pathologic conditions in the breast with the hope of proving or disproving any relationship between chronic mastitis and carcinoma. In so doing the problem of the histogenesis was uppermost. In conducting this investigation 1000 breasts, including all chronic pathologic conditions, were studied. Many sections were made from all portions of the gland, including both normal and pathologic portions. These sections were not only submitted to microscopic study but were studied photographically. Carcinoma being a growth which is intimately associated with glandular cells, it was thought best to study such cells in the structural and functional unit (acinus) of the organ. It was found that the unit or acinus was lined in the resting condition and that of chronic mastitis by two layers of cells, their inner layer consisting of cuboidal or columnar cells and the outer of spheroidal or ovoidal cells, the latter lying adjacent to the mammary stroma.

The embryologic origin of these two layers was studied and it was found that both were derived by means of a hyperplasia and downward growth of the cells from the stratum germinativum of embryonic skin.<sup>20</sup> It was therefore supposed that the outer layer was the stratum germinativum of the secretory cells of the acinus. Photomicrographs of acini from all portions of the glands grouped themselves into three distinct histologic groups (Fig. 1). They were called primary, secondary, and tertiary cytoplasia, respectively.<sup>20</sup>

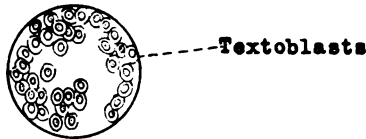
The clinical significance of these histologic pictures has been of great economic importance to the clinician, the surgeon and the pathologist. The first certainly is a benign condition, the third is, without question, the condition which has been recognized as carcinoma, and the second is not so easily interpreted; it was, therefore, spoken of as questionable in spite of the fact that the intra-acinic cells are frequently identical morphologically with the cells of the third condition.<sup>20 21</sup> At the time of preliminary investigation I had confidence in the old criterion for histologic malignancy which utilizes the basement membrane (*membrana propria*) as the line of demarcation between a malignant and a benign condition; the cells of secondary cytoplasia are within the histologic bounds of benignancy despite the fact that they are morphologically identical with those of carcinoma. From a clinical or practical standpoint, I have been convinced that all mammary gland-bearing tissue presenting such a picture should be removed, leaving, perhaps, the pectoral muscles and axillary lymphatic glands. I have not felt

justified in advising the removal of the breast, muscles, and axillary glands by means of a radical operation. Rules have been established on this basis and subsequent postoperative histories have justified, so far, the legitimacy of such a conservative operation.<sup>22</sup>

#### PRIMARY CYTOPLASIA



#### SECONDARY CYTOPLASIA



#### TERTIARY CYTOPLASIA



FIG. 1.—Diagrammatic representation of the original structural facts found in the mammary acinus. In primary cytoplasia the milk-producing cells (lactocytes) belong to the general group of tissue-cells (textocytes). The regenerative cells which constitute the stratus germinativum for the lactocytes have been called lactoblasts and belong to the general reserve cells of the body which have been called textoblasts. In primary cytoplasia the lactoblasts (textoblasts) have disappeared and there is an hyperplasia of the lactoblasts (textoblasts). In tertiary cytoplasia the lactoblasts (textoblasts) have migrated (in a biologic sense) from their normal acinic habitat.

The three conditions, however, are of greatest interest from a biological standpoint<sup>16 17</sup> since they furnish an opportunity for the study of the relations of cytostructure and relationship to cytofunction. From this point of view it has been clearly seen that nature has provided reserve cells (the cells of the outer row) for the secreting cells (the cells of the inner row) which in the course of their existence as a part of the communistic organism might be destroyed. These reserve cells (textoblasts) form the outer layer

that is so much in evidence in chronic mastitis, which is a definite destructive condition.

The three histologic pictures represent hypertrophy, hyperplasia, and migration, which are the fundamental protective activities of all living matter throughout nature, the first representing hyperactivity, the second, reproduction, and the third, change of environment. The biologic cause of this apparent sequence of cytoaction is undoubtedly destruction or the presence of a destructive agent or agents. Some thing, or some environmental condition, or both, call forth protective hyperactivity on the part of the textoblasts. In the second histologic picture actual, partial, or complete destruction of textocytes calls forth a hyperplasia or reproduction of textoblasts. Although the destructive factor is unknown, it is of sufficiently low virulence not to destroy the reserve cells and sufficiently virulent to prevent their complete differentiation and specialization into textocytes. The textoblasts remain spheroidal or ovoidal and do not remain in their normal acinic arrangement although they may still retain their acinic habitat.

During all investigations no attention was paid to the specific agent or agents causing these reactions because it was thought best to study primarily the biologic factor or factors.

The three fundamental biologic reactions to destruction have been found to occur not only in relation to the specific tissue of the breast but also in relation to the specific tissues of the prostatic gland, skin, hair follicles, stomach, lymphatic glands, blood, bone, cartilage, and connective tissue.<sup>23</sup> In all of these chronic destruction of the specific tissues calls forth hypertrophy, hyperplasia, and sometimes migration of the reserve cells.

Although these reactions may seem new in reference to human pathology they are well known to biologists who have made a study of reaction to destruction. In fact many biologists are of the opinion that exposure of living matter to destructive factors has led to such adaptive potentialities which are the factors of safety in the structure and function of all forms of life; nature has been just as efficient in her defensive preparation in the construction of the human body.

It may be stated as a biologic law that hypertrophy, hyperplasia, and migration are stimulated primarily by destruction. These phenomena are the effects of which destruction is the cause.

In nature the specific agent of destruction is rarely, if ever, anticipated. It makes no difference whether the leaf, stem, or branch of a geranium plant is pinched off, broken off, cut off, eaten off or burned off; the main factor is the destruction. In the mammary gland destruction is the main factor as it is with the other tissues which have been studied.

The reactionary cells of the three conditions described above are

apparently normal cells which answer the structural description of normal cells as found any place in nature. Their relation to the communistic organization of cells is their principal abnormal or pathologic characteristic.

Many authorities have considered the cells of neoplasms to be intrinsically and structurally abnormal without positively demonstrating that such cells are even structurally abnormal. Practically every authority, including biologists, who speaks or writes upon the subject of abnormality of neoplastic cells quotes Hansemann<sup>10</sup> and Galleotti,<sup>9</sup> who described atypical mitoses and other unusual conditions in the cells of malignant neoplasms. As a result of my own failure to find in perfectly fresh and unfixed cells such atypical mitosis as a characteristic of neoplastic cells it has seemed that the basis of irregular mitosis as described by the authorities mentioned is probably not so much a question of their actual occurrence as it is a question of their being due to artefacts, poor fixation, unusual planes through mitotic figures, or swollen, distended or disintegrating cells. The work of von Hansemann and Galleotti might well be repeated utilizing perfectly fresh, unfixed material, the cells of which should be studied from the standpoint of orthographic projection and cellular disintegration.

In so far as cancer (a migratory hyperplasia) is concerned, my observations have revealed a biologic reaction which is malignant only in so far as it destroys the communistic organization of cells.

In all of the tissues which have been studied there is a normal reserve stratum or focus, the cells of which exist in a partially differentiated or undifferentiated condition. In the human body, however, some primitive tissues possessing reproductive potentiality exist. The cells of the nervous system, muscular system, endothelial system and perhaps the cells lining the alimentary canal and others belong to this group. This may account for the failure to find the reserve cells for some of the specific tissues of the body. Whether or not there be reserve cells does not alter the biologic phenomena because all cells possessing the power of regeneration react in the same way. Under certain conditions of destruction such cells become hypertrophic, hyperplastic and migratory. These phenomena, which are very evident in the reactions of cells of the body and in the rest of nature, demand descriptive names.<sup>24</sup> As has been stated, they have been called primary, secondary and tertiary reactions or conditions (cytoplasias). It seems logical to attempt to describe the reactions of certain tissues by adding the root of the name of the reacting tissues—thus the conditions in the glandular epithelium (adenotex) of the breast were described as:

Primary	}	adeno-cytoplasia or expando-	restauro-	}	adeno-cytoplasia.
Secondary			migro-		
Tertiary					

This terminology expresses the biologic phenomena, the histologic pictures and cytologic conditions of cytheregeneration of a specific tissue without stating the stage of cytodifferentiation. Primary adenocytoplasia represents the ordinary attempt at restoration of the specific glandular tissue, secondary adenocytoplasia represents

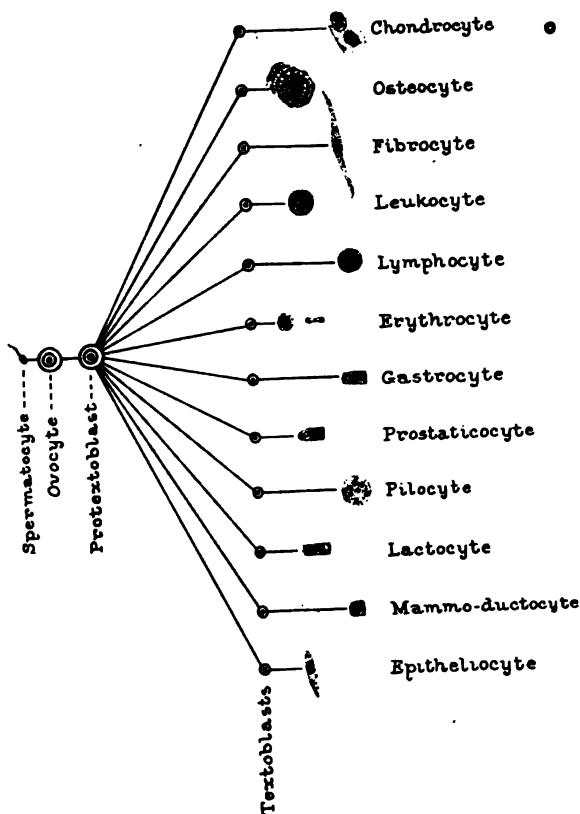


FIG. 2.—Diagrammatic representation of the embryologic evolution of the tissue cells (textocytes) the reserve cells (textoblasts) of which have been studied. After fertilization of the ovocyte, the biological phenomena of segmentation, prodifferentiation and differentiation occur. The cells produced during these phenomena have been called prototextoblasts, textoblasts, and textocytes. This diagram represents the second stage in the evolution of the structural basis for a biologic conception. Figure 1 is the first stage and Figure 3 is the third stage.

an expansive overgrowth of the reserve cells of the glandular tissue and the tertiary adenocytoplasia represents a migratory hyperplasia. The first condition is clinically a benign reaction since it is but the process of repair, the second is uncertain as to benignancy or malignancy because no one can foretell whether the hyperplastic undiffer-





In view of the fact that this conception is biologically logical and expressive of what actually happens in the evolution of this one tissue, the accompanying diagram for all tissues which have been studied was constructed (Fig. 2).

Instead of adhering to the old idea of classifying tissues into epiblastic, mesoblastic and hypoblastic tissues, as the text-books have done, it seems that the human body is made up of as many specific and differentiated tissues as there are different kinds of cells with different morphology and function in the body. As a result of structural and functional segmentation of the fertilized ovum there arise many tissues which deserve just as much recognition, as entities, as do the specific tissues described in text-books of histology.

One cannot make progress in constructing a biologic conception of neoplasms unless all the known tissues receive names and have their morphologic and perhaps functional characteristics appreciated. It has therefore been deemed essential to name these tissues and establish their biologic relationships. Based upon their morphology and function each tissue should receive a name (Fig. 3) which differentiates it from all other tissues in the body and makes it an entity to be dealt with from the standpoint, not only of morphology and function, but of cytotransformation and differentiation certain phases and combinations of which produce benign or malignant neoplastic conditions.

The three reactions may be expressed therefore as follows:

Primary Secondary Tertiary	}	. . .	Adeno-	}	Cytoplasia.
			Audito-		
			Cardiomyo-		
			Chondro-		
			Endothelio-		
			Epithelio-		
			Erythro-		
			Fibro-		
			Glio-		
			Gusto-		
			Leiomyo-		
			Leuko-		
			Lipo-		
			Lympho-		
			Melano-		
			Myo-		
			Myxo-		
			Neuro-		
			Odoro-		
			Osteo-		
			Perithelio-		
			Pilo-		
			Rhabdomyo-		
			Sebo-		
			Tactilo-		
			Tendo-		
			Visio-		
			Etc.		

There is one other important phenomenon in connection with cytoplasia to be described, *i. e.*, cytodifferentiation. In so far as the human organism is concerned the cells which constitute the tissues are differentiated in three degrees during their evolution. The textoblasts which are to form tissues first arrange themselves according to the general direction of the adult tissue (primary differentiation); if the textocytes are to cover a surface, the textoblasts arrange themselves first in a plane; if they form an acinus, they arrange themselves in the form of the lining surface of an acinus. In the first stage or primary differentiation, the cells are still undifferentiated in so far as their morphology is concerned. The second stage (secondary differentiation) consists of the establishment of tissue cytopolarity (textocytolarity) and the third (tertiary differentiation) consists of normal alignment, normal polarity and normal appearance of cytoplasm and nucleoplasm. Complete differentiation (the third degree) plus normal function produces an accessory tissue or if more than one tissue be involved, an accessory organ.

This phenomenon of differentiation is not only one which is seen during the evolution of normal tissues but one which plays an important role in the evolution and life-history of neoplasms.

If the cells of the stage of cellular regeneration (cytoregeneration) which has been called secondary cytoplasia become differentiated to the third degree a benign neoplasm is formed. It is thus that fibromas, adenomas, fibromyomas, adenomyomas and other benign neoplasms occur. There is an expansive overgrowth of the fibro-, myo-, and adenoblasts which become differentiated either separately or in combination to the point of morphologic identity with their respective textocytes. It is true that in many such neoplasms the process of expansive overgrowth continues gradually by virtue of the existence of some remaining textoblasts, which become readily differentiated.

In some conditions of secondary and migratory cytoplasia differentiation does not occur or at least never reaches beyond the first and second stages. This is true of the so-called malignant neoplasms. Complete differentiation is apparently impossible. If it occurred in tertiary cytoplasia accessory tissues would appear in malignant neoplasms.

Upon examination of tissues, in so far as cytoregeneration and differentiation are concerned, one must determine the following facts:

Location.	Gross form.	Biological and clinical reaction.	Tissue involved.	The degree of differentiation.
capito- collo- cranio- auriculo- naso- linguo- labio- laryngo- etc.	<div> <div>circumscribed</div> <div>diffuse</div> <div>cystic</div> <div>extracystic</div> <div>ductal</div> <div>intraductal</div> <div>periductal</div> <div>papillary</div> <div>polypoid</div> <div>ulcerated</div> </div>	<div> <div>Primary</div> <div>Secondary</div> <div>Tertiary</div> </div>	<div> <div>audito-</div> <div>adeno-</div> <div>cardiomyo-</div> <div>chondro-</div> <div>endothelio-</div> <div>epithelio-</div> <div>erythro-</div> <div>fascio-</div> <div>fibro-</div> <div>glio-</div> <div>gusto-</div> <div>leiomyo-</div> <div>leuco-</div> <div>lipo-</div> <div>lympho-</div> <div>melano-</div> <div>myo-</div> <div>myxo-</div> <div>neuro-</div> <div>odoro-</div> <div>osteo-</div> <div>perithelio-</div> <div>pilo-</div> <div>rhabdomyo-</div> <div>sebo-</div> <div>tactilo-</div> <div>tendo-</div> <div>visio-</div> <div>x-</div> </div>	<div> <div>Cytoplasmia with or without</div> <div> <div>primary,</div> <div>secondary,</div> <div>tertiary</div> <div>differentiation.</div> </div> </div>

The terminology which is expressive of these facts may be abbreviated in the following manner:

Location.	Gross form.	Degree of biological and clinical reaction.	Tissue.	Degree of differentiation.
capito- collo- cranio- auriculo- naso- linguo- labio- laryngo- etc.	<div> <div>circumo-</div> <div>diffuso-</div> <div>cysto-</div> <div>extracysto-</div> <div>intracysto-</div> <div>ducto-</div> <div>intraducto-</div> <div>extraducto-</div> <div>papillo-</div> <div>polypo-</div> <div>ulcero-</div> </div>	<div> <div>1</div> <div>2</div> <div>3</div> </div>	<div> <div>audito-</div> <div>adeno-</div> <div>cardiomyo-</div> <div>chondro-</div> <div>endothelio-</div> <div>epithelio-</div> <div>erythro-</div> <div>fascio-</div> <div>fibro-</div> <div>glio-</div> <div>gusto-</div> <div>leiomyo-</div> <div>leuco-</div> <div>lipo-</div> <div>lympho-</div> <div>melano-</div> <div>myo-</div> <div>myxo-</div> <div>neuro-</div> <div>odoro-</div> <div>osteo-</div> <div>perithelio-</div> <div>pilo-</div> <div>rhabdomyo-</div> <div>sebo-</div> <div>tactilo-</div> <div>tendo-</div> <div>visio-</div> <div>x-</div> </div>	<div> <div>cytoplasmia</div> <div> <div>1</div> <div>2</div> <div>3</div> </div> <div>differentiation</div> </div>

These same facts may be symbolically expressed in the following manner:\*

capito-	{	Δ	{	1	{	Au	{	1	{	D.
collo-		Λ		2		Ad				
cranio-		Ο		3		Cm				
auriculo-		Θ				Ch				
naso-		Φ				En				
linguo-		Τ				Ep				
labio-		Π				Er				
laryngo-		Υ				Fa				
etc.		Ρ				Fi				
		Ω				Gl				
		Σ				Gu				
						Lm				
			Le							
			Li							
			Ly							
			Me							
			My							
			Mx							
			Ne							
			Od							
			Os							
			Pe							
			Pi							
			Rm							
			Se							
			Ta							
			Te							
			Vi							
			X							

The symbolic terminology has been utilized on account of brevity and accuracy in expressing the facts relative to regeneration in its relation to neoplasia. If one wishes to describe what has been called a fibro-adenoma of the breast it may be written: Mammo- $\Delta 2(\text{fi ad})3\text{D}$ , which expresses, to one familiar with the key, the location, gross form, degree of cytoplasmia, tissues involved and the degree of cytodifferentiation. Malignancy and benignancy depend

\* In this key the root of the accepted His anatomic nomenclature expresses the organic location; the Greek capitals represent the gross form or manifestation of the neoplastic condition; the numerals 1, 2 and 3 indicate the biologic stage of cyto-activity (hypertrophy, hyperplasia, and migratory hyperplasia); the first two letters of the roots of accepted names of specific tissues are utilized symbolically in a similar manner to that utilized in chemical symbolic terminology; the numerals 1, 2, 3, before the capital D, express the degree of differentiation. The Greek letters have the following symbolic meaning:

- |                    |   |                                |
|--------------------|---|--------------------------------|
| $\Delta$ delta     | = | circumscribed or encapsulated. |
| $\Lambda$ lambda   | = | diffuse or non-encapsulated.   |
| $\bigcirc$ omicron | = | cystic.                        |
| $\Theta$ theta     | = | intracystic.                   |
| $\Phi$ phi         | = | extracystic.                   |
| $\tau$ tau         | = | ductal.                        |
| $\Pi$ pi           | = | intraductal.                   |
| $\Psi$ psi         | = | extraductal.                   |
| $\rho$ rho         | = | papillary.                     |
| $\Omega$ omega     | = | polypoid                       |
| $\Sigma$ sigma     | = | ulcerated.                     |

on at least two factors in so far as the tissues and their reactions are concerned. These are the biological reactions of hypertrophy, hyperplasia, migration and degree of cytodifferentiation. Undoubtedly there are other factors such as lymphocytic infiltration, fibrosis, hyalinization, location, encapsulation and perhaps conditions which are as yet unknown, but these factors are not sufficiently understood to be placed in our present terminology.

The main facts in any compound terminology are universality, simplicity, accuracy, brevity, and expressiveness of structural and functional facts and relationships. In the compound terminology just expressed, structure, characteristic functions, biostructural relationships and clinical values are briefly, systematically, simply and accurately portrayed. This, unfortunately, cannot be said of the compound and simple terminology which is expressed in text-books, taught to twentieth century students and practised by pathologists in all parts of the world. This new terminology is perhaps not perfect any more than Lavoisier's improvements in chemical terminology were perfect but it is an improvement and will serve as a basis for more perfect terminology in the future.

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## THE PROGNOSTIC VALUE OF THE CREATININE OF THE BLOOD IN NEPHRITIS.\*

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ATTENTION has been called in several communications<sup>1</sup> to the prognostic value of the creatinine content of the blood in cases of advanced nephritis. We now have a much larger series of cases, indicating the value of this test, and it has been thought worth while to briefly summarize all our data on this subject.

In our studies on nitrogen retention it was soon noted that the creatinine of the blood was appreciably increased only after considerable retention of urea had already taken place and the nephritis was rather far advanced. It was further observed that those cases in which the creatinine had risen above 5 mg. per 100 c.c. of blood rarely showed any marked improvement, and almost invariably died within a comparatively limited time. On the other hand a number of cases were encountered in which there was a marked

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<sup>1</sup> Myers and Lough: *Arch. Int. Med.*, 1915, xvi, 536; Chace and Myers: *Jour. Am. Med. Assn.*, 1916, lxvii, 929.

retention of urea, but in which the creatinine was below this figure. In many of these cases improvement took place.

Theoretically, the amount of the increase of the creatinine of the blood should be a safer index of the decrease in the permeability of the kidney than the urea, for the reason that creatinine on a meat-free diet is entirely endogenous in origin and its formation (and elimination normally) very constant. Urea, on the other hand, is largely exogenous under normal conditions and its formation consequently subject to greater fluctuation. For this reason it must be evident that a lowered nitrogen intake may reduce the work of the kidney in eliminating urea, but cannot affect the creatinine to any extent. Apparently the kidney is never able to overcome the handicap of a high creatinine accumulation. It would seem that creatinine, being almost exclusively of endogenous origin, furnishes a most satisfactory criterion as to the deficiency in the excretory power of the kidneys and a most reliable means of following the terminal course of the disease, though it should be noted that urea, being largely of exogenous origin, is more readily influenced by dietary changes, and therefore constitutes a more sensitive index of the response to treatment.

The view that uremic symptoms are due directly to retained urea, uric acid or creatinine has now long been regarded untenable, although the recent work of Hewlett, Gilbert and Wickett<sup>2</sup> is of interest in this connection. They found that the administration to normal subjects of sufficient urea to produce a blood concentration of 150 mg. per 100 c.c. (70 mg. of urea nitrogen) resulted in symptoms of bodily and mental asthenia. They state: "This by no means excludes the possibility that other substances may play a rôle in producing the symptoms of this type of uremia, and, indeed, the fact that animals die only when extraordinary doses of urea are administered suggests that the fatal outcome of asthenic uremia in man may be due to other substances than urea." That urea and uric acid may break up in the body into anything more toxic seems improbable, but the possibility that retained creatinine may give rise to the toxic methylguanidine lends further interest to creatinine in this connection. In 1912 W. F. Koch<sup>3</sup> isolated methylguanidine from the urine of animals dying from parathyroid tetany. More recently, Paton and his co-workers<sup>4</sup> have demonstrated that there is a marked increase in the amount of guanidine and methylguanidine in the blood and urine of dogs after the removal of the parathyroids and in the urine of children suffering from idiopathic tetany. Foster<sup>5</sup> has been able to isolate a very toxic substance from uremic blood in the form of a gold salt. This substance when injected into

<sup>2</sup> Arch. Int. Med., 1916, xviii, 636.

<sup>3</sup> Jour. Biol. Chem., 1912, xii, 313.

<sup>4</sup> Quart. Jour. Exper. Physiol., 1917, x, 203-382.

<sup>5</sup> Tr. Assn. Am. Phys., 1915, xxx, 305.

animals produces symptoms similar to those noted in uremia. Although Foster did not obtain sufficient of this compound to identify it, it is significant that guanidine compounds form very characteristic gold salts. These observations lend support to the view that the retention of creatinine may possess special significance in uremia. This topic is one upon which we are endeavoring to obtain further information.

As the result of recent studies on acidosis,<sup>8</sup> it is now recognized that nearly all advanced cases of nephritis show a considerable degree of acidosis,<sup>7</sup> probably due to a retention of (acid) phosphate.<sup>2</sup> In this connection it is of interest that Watanabe<sup>9</sup> has found that the administration of guanidine to animals induces a condition of severe acidosis with the retention of phosphate and a decrease of calcium in the blood. It may be mentioned that a few unpublished analyses which we have made on terminal cases of nephritis show a marked decrease in the calcium content of the blood.

Turning to the more practical side of this question, it is our opinion that in these advanced cases of nephritis the blood creatinine furnishes a more reliable prognosis than any other test that we possess. Our observations in support of this statement are furnished in the tables below. Figures are likewise included for urea and phenol-sulphonaphthalein. Although, as a rule, several blood analyses were carried out during the course of the disease, only one set has been recorded in Table I. This has generally been the last observation obtained before death or previous to the patient's leaving the hospital.

**METHODS EMPLOYED.** Inasmuch as there has recently been some discussion of the absolute accuracy of the creatinine estimation in blood, it may be well to make a few remarks regarding this determination. Prior to the publication by Folin of his method for this determination we had already carried out a few estimations of this substance in blood,<sup>10</sup> utilizing suggestions made by Shaffer and Reinoso<sup>11</sup> several years previously for the estimation of creatinine in dilute solutions. With the publication of Folin's paper<sup>12</sup> we adopted his method for the most part, except that we still continued to carry out the preliminary dilution of the blood with water rather than picric acid solution, for the reason that we regarded this the preferable way of analyzing the whole blood. Furthermore, we have always combined the creatinine and blood-sugar<sup>13</sup> estimations, as

<sup>8</sup> Van Slyke and Cullen: Jour. Biol. Chem., 1917, xxx, 289; Van Slyke: *ibid.*, p. 347.

<sup>7</sup> Whitney: Arch. Int. Med., 1917, xx, 931.

<sup>6</sup> Marriott and Howland: *Ibid.*, 1916, xviii, 708.

<sup>9</sup> Watanabe: Jour. Biol. Chem., 1918, xxxvi, 531.

<sup>10</sup> Myers and Fine: Proc. Soc. Exp. Biol. Med., 1914, xi, 132, and Chemical Composition of the Blood in Health and Disease, reprinted from The Post-Graduate, 1914-15, p. 19.

<sup>11</sup> Jour. Biol. Chem., 1910, vii, proceedings, p. xxx.

<sup>12</sup> *Ibid.*, 1914, xvii, 475.

<sup>13</sup> Myers and Bailey: *Ibid.*, 1916, xxiv, 147.



this is also a suitable preliminary step in the case of the sugar estimation.

Our technic has been as follows: To 20 c.c. of distilled water in a 50 c.c. centrifuge tube are added 5 c.c. of the well-mixed oxalated blood. This is then stirred with a glass rod until the blood is thoroughly hemolyzed, after which about 1 gram of dry picric acid (sufficient to completely precipitate the proteins and render the solution saturated) is added. The mixture is thoroughly stirred until it is uniformly yellow and then at intervals for twenty to thirty minutes, after which it is centrifuged and filtered. Sufficient filtrate is obtained for the estimation of both the creatinine and the sugar. To 10 c.c. of this filtrate is added 0.5 c.c. of 10 per cent. sodium hydroxide and a similar amount of alkali added to each of three standards (10 c.c. of standard creatinine in saturated picric acid, containing 0.3, 0.5 and 1.0 mg. creatinine to 100 c.c. of picric acid). Pure creatinine is readily prepared by the admirable method of Benedict.<sup>14</sup> A standard solution of creatinine, 1 mg. to 1 c.c., is kept in 0.1 N hydrochloric acid, and from this the various solutions are prepared with saturated picric-acid solution. A standard is selected which approximates the color intensity of the unknown, the prism being set at the 10 or 15 mm. mark. With bloods showing over 5 mg. of creatinine it has been customary to further dilute the blood filtrate with saturated picric-acid solution, so that the color when developed would match, *e. g.*, between the 7 and 13 mm. mark when the standard was set at 10. Originally we allowed ten minutes for the development of the color, but owing to the observations of Hunter and Campbell<sup>15</sup> this has been reduced to eight minutes. We have experienced comparatively little difficulty with color-forming substances in the picric acid, although some of our picric acid has been purified by the method of Folin and Doisy.<sup>16</sup>

In a paper dealing with the creatinine content of the blood of different animals, Wilson and Plass<sup>17</sup> pointed out that the results were higher in whole blood than in plasma. They also found that using alumina cream as the protein precipitant, a method which we had previously employed in determining creatinine in muscle,<sup>18</sup> slightly lower results were obtained than when the Folin method was employed. Hunter and Campbell<sup>19</sup> have recently made a more extensive study of this question. Although they originally made their creatinine estimations on laked blood, following our suggestion, they have recently obtained data which tend to show that these results are somewhat too high (particularly in normal blood), owing to an interference in the color development on the part of some constituent in the corpuscles. With plasma, however, the results

<sup>14</sup> Myers and Bailey: Jour. Biol. Chem., 1914, xviii, 183.

<sup>15</sup> Ibid., 1917, xxxii, 195.

<sup>17</sup> Ibid., 1918, xxxv, 513.

<sup>18</sup> Myers and Fine: Ibid., 1914, xvii, 65.

<sup>16</sup> Ibid., 1916-17, xxviii, 349.

<sup>19</sup> Loc. cit.

appear to be approximately correct. Greenwald and McGuire<sup>20</sup> have likewise studied this question. They employed two methods of precipitating the blood proteins aside from picric acid, viz., colloidal iron and trichloroacetic acid. Their results with these methods of precipitation were slightly lower than with the Folin method, although not uniformly so. In carrying out the picric-acid precipitation they followed our suggestion in laking the blood first, but regarded shaking necessary to render the solution saturated. In our hands it has been found possible to obtain a much more homogeneous mixture with the aid of a stirring rod than with shaking alone. Denis<sup>21</sup> has recently suggested still another method of precipitating the proteins. She employs metaphosphoric acid apparently to very excellent advantage, inasmuch as she has been able to utilize the preliminary precipitation for an apparently satisfactory estimation of creatine as well. Her results for creatinine, though slightly lower, differ but little from those obtained by the Folin method on normal blood.

We have taken occasion to compare the creatinine content of the blood with that of the plasma in cases of marked retention, and have found the figures in the plasma about 10 per cent. lower than in the whole blood, a difference which we scarcely believe to be entirely due to the intervening substance in the corpuscles.<sup>22</sup> Although, as Hunter and Campbell have pointed out, the creatinine estimation in normal blood is probably more accurate in plasma than in whole blood, the absolute accuracy of the estimation in whole blood is much greater with pathological than normal values, i. e., the accuracy increases with its clinical importance.

The urea estimations were made by a modified Marshall-Van Slyke method, essentially as described by Myers and Fine.<sup>23</sup> The enzyme used is that derived from the jack bean. The Nessler solution employed at present is from a very satisfactory formula furnished us by Drs. Benedict and Bock, which contains 100 grams of mercuric iodide, 70 grams of potassium iodide and 100 grams of sodium hydroxide per liter of solution. The phthalein injections were made intramuscularly in practically all cases. The CO<sub>2</sub> combining power recorded on a number of the cases under the heading of remarks was made according to the Van Slyke method.<sup>24</sup> In the last three columns of Table I are recorded the length of time under observation and present condition, together with a few remarks pertinent to the history of the individual cases. Unless otherwise noted the clinical diagnosis was chronic interstitial nephritis.

<sup>20</sup> Myers and Fine: Jour. Biol. Chem., 1918, xxxiv, 103.

<sup>21</sup> Ibid., 1918, xxxv, 513.

<sup>22</sup> Hunter and Campbell: Jour. Biol. Chem., 1917, xxxii, 195.

<sup>23</sup> Arch. Int. Med., 1916, xvii, 570.

<sup>24</sup> Cullen and Van Slyke: Jour. Biol. Chem., 1917, xxx, 289; Van Slyke: Ibid., 347.

**DISCUSSION.** The 100 cases<sup>25</sup> recorded in Table I would seem to be a sufficiently large series to enable one to arrive at fairly definite conclusions. In an earlier communication by Myers and Lough,<sup>26</sup> dealing with the prognostic value of the creatinine of the blood in nephritis, the statement was made: "Creatinine values from 2.5 to 3 mg. may be viewed with suspicion; figures from 3 to 5 mg. regarded as decidedly unfavorable, while over 5 mg. probably indicate an early fatal termination." Although the great majority of cases without kidney involvement show creatinine figures on the whole blood below 2.5 mg. per 100 c.c., occasionally figures as high as 3.5 mg. are encountered that are not readily explained. It may be noted, however, that a slight retention of creatinine (figures between 3 and 4 mg.) occurs in syphilis, certain heart conditions, and in some advanced cases of diabetes. Creatinine figures above 3.5 mg. are almost invariably accompanied by an appreciable urea retention and this is generally true of those above 3 mg. Many of the cases below 4 mg. show improvement, but with over 4 mg. the reverse is the case. It would appear from this that an appreciable retention of creatinine, *i. e.*, over 4 mg., does not occur until the activity of the kidneys is greatly impaired.

As will be noted in Table I, the 100 cases are arranged in the order of the magnitude of the blood creatinine. The series includes all cases with over 5 mg. creatinine which have come under our observation since March, 1914, with the exception of 3 patients whom we have been unable to trace and who are presumably dead. It will be observed that the first 73 cases in the series are all dead, with the exception of Case 59 (P. H.), whose condition remains essentially unchanged at the present writing. Sixty of these first 73 cases died within two months after they came under our observation, although the remainder lived for periods varying from three months to one year. It may be of interest to note that Case I (W. F.) died from bichloride poisoning while Cases 52 (H. B.) and 64 (E. H.) suffered from double polycystic kidney. Even among the first 73 cases of the series there were many who were able to be up and about and some who showed considerable clinical improvement. It was in these cases that we believe the blood creatinine gave us a particularly good prognostic insight into the true nature of the condition.

<sup>25</sup> Most of these cases were patients in the medical wards of the hospital, although some were patients in the urological and surgical wards. We are especially indebted to Drs. Chace, Kast and Halsey of the Medical Department, Dr. Squier of the Urological Department, and Drs. Erdmann and Lloyd of the Surgical Department for their coöperation in helping us to obtain these data. In following the different cases during the past five years, we are indebted to the following former members of the house staff, Drs. Lough, Nacey, Donaldson and Costen.

<sup>26</sup> *Loc. cit.*

TABLE I.—THE PROGNOSTIC VALUE OF THE CREATININE OF THE BLOOD IN NEPHRITIS.\*

Case.	Date.	Age.	Sex.	Blood analyses.			Phthalein, two-hour output, per cent.	Time under observation.	Present condition.	Remarks.
				Creatinine, mg. to 100 c.c.	Urea N.	mg. to 100 c.c.				
1. W. F.	Nov. 20, 1914	25	M.	33.3	240		...	1 mo.	Dead	Case of bichloride poisoning; died 16 days after this observation; uræmic symptoms appeared one week previous to death, although the creatinine had then fallen to 14.8 mg.
2. E. M.	Dec. 21, 1915	39	M.	28.6	186		0	3 wks.	"	Able to be up and about and did not realize the seriousness of his condition when first admitted three weeks before this examination, although his creatinine was then 17.5 mg.; died Dec. 25, his CO <sub>2</sub> combining power having then fallen to the low figure of 12, despite treatment.
3. A. C.	Oct. 11, 1917	53	M.	22.5	106		0	2 wks.	"	Marked dyspnea, CO <sub>2</sub> on Oct. 15, 25; died nine days after this examination.
4. S. H.	June 25, 1915	37	M.	22.2	262		0	5 wks.	"	Admitted to hospital on May 8, complaining of stomach trouble; after phlebotomy on June 26 patient was much brighter and pulse better; died on June 28.
5. T. D.	Mar. 23, 1915	34	M.	20.5	152		4 to 0	2 mos.	"	Disinæes; retinal hemorrhages; in hospital two months; died Mar. 23.
6. I. D.	Jan. 3, 1915	17	F.	20.0	209		0	1 mo.	"	Moderate dilatation of heart; died Jan. 4.
7. P. J.	Feb. 14, 1916	43	M.	20.0	162		0	4 days	"	CO <sub>2</sub> combining power on this date 43; extreme dyspnea; bilateral decapsulation; died about two and a half hours after operation.
8. L. R.	Aug. 2, 1916	25	F.	20.0	108		Trace	3 wks.	"	Generalized edema; also lobar pneumonia; CO <sub>2</sub> 36 Aug. 4, date of death.
9. E. D.	June 26, 1917	53	F.	19.8	114		0	2 wks.	"	Marked dyspnea; CO <sub>2</sub> on admission 27; after rectal administration of 2 per cent. NaHCO <sub>3</sub> June 26 the CO <sub>2</sub> rose to 76; died three days later in uremia.
10. N. W.	Sept. 4, 1918	19	F.	19.2	164		0	2 wks.	"	Admitted Aug. 29, CO <sub>2</sub> Sept. 4, 31; removed against advice Sept. 12; died at home in convulsions the following day.

11. E. L.	Mar. 28, 1916	20	F.	18.9	141	0	2 wks.	"	Clinical diagnosis, acute parenchymatous nephritis; CO <sub>2</sub> this date 46; died the following day.
12. R. A.	Nov. 6, 1916	30	F.	18.7	68	...	1 wk.	"	Acute hemorrhagic nephritis, with complete suppression of urine; bilateral decapsulation Nov. 4; CO <sub>2</sub> then 38; lived three days after operation, two specimens of urine being obtained.
13. M. M.	May 19, 1916	40	F.	18.3	246	...	2 days	"	Admitted May 18 and died two days later; also chronic endocarditis.
14. M. B.	Jan. 3, 1919	48	M.	18.1	172	...	1 wk.	"	Admitted Dec. 29; discharged unimproved Jan. 4; died at home next day.
15. E. P.	Dec. 12, 1916	34	F.	17.6	85	0	2 wks.	"	Admitted Dec. 6, also purpura hemorrhagica; CO <sub>2</sub> Dec. 12, 32; left hospital against advice Dec. 14 and died at home Dec. 19.
16. E. C.	April 11, 1915	50	F.	16.7	236	0	2 days	"	Died this date, two days after admission.
17. W. O. C.	Mar. 8, 1914	33	M.	16.6	182	Trace	7 wks.	"	Marked cyanosis and dyspnea; died the day following this observation.
18. M. K.	May 13, 1914	42	M.	14.7	170	...	3 wks.	"	Diagnosis, chronic diffuse nephritis; marked edema and cyanosis; coma; double decapsulation this date; patient died during operation.
19. K. K.	Mar. 26, 1915	39	F.	14.7	148	0	1 wk.	"	Considerable cardiac hypertrophy; died Mar. 27, one week after admission.
20. J. H.	May 16, 1916	29	M.	14.7	77	...	2 wks.	"	Admitted May 1; died May 18.
21. W. C.	Mar. 20, 1917	24	M.	14.5	123	Trace	2 wks.	"	Bilateral decapsulation Mar. 22, died five days later.
22. M. P.	Jan. 3, 1917	25	M.	14.4	141	0	2 wks.	"	Albuminuric retinitis with almost complete loss of vision.
23. A. M.	Sept. 25, 1918	44	M.	13.5	147	0	2 mos.	"	CO <sub>2</sub> 31 Dec. 26, but administration of bicarbonate brought this up. It was 44 Jan. 5, the date of death.
24. E. P.	Mar. 1, 1916	40	F.	12.7	116	0 to 1	3 mos.	"	Admitted Sept. 16 and died Nov. 18; chief complaint on admission, weakness and loss of appetite; CO <sub>2</sub> 32 on admission.
								"	Died Mar. 25, three months after first observation and six weeks after being removed from hospital against advice; retinal hemorrhages.

\* Strictly normal values for the creatinine of the blood may be given as 1 to 2 mg. per 100 c.c., urea N, 12 to 15 mg., uric acid 2 to 3 mg., sugar 0.09 to 0.12 per cent., and CO<sub>2</sub> combining power 50 to 75 c.c. per 100. Unless patients are under specially controlled conditions, deductions are not drawn from individual figures which do not exceed 3.5 mg. creatinine, 20 mg. urea N, 4.5 uric acid, 0.15 per cent. sugar or CO<sub>2</sub> combining power that is below 45 c.c.

TABLE I.—THE PROGNOSTIC VALUE OF THE CREATININE OF THE BLOOD IN NEPHRITIS (continued).

Case.	Date.	Age.	Sex.	Blood analyses.		Phthalate, two-hour output, per cent.	Time under observation.	Present condition.	Remarks.
				Creatinine, mg. to 100 c.c.	Urea, N				
25. A. N.	Mar. 22, 1918	27	F.	12.6	110	0	3½ mos.	Dead	Discharged Mar. 30; clinically improved, albuminuria retinitis, reconstituted Apr. 27, no change in blood; died May 25; May 22, urea N 148, creatinine 17 and CO <sub>2</sub> combining power 12.
26. A. L.	July 25, 1918	52	F.	12.6	78	...	5 days	"	Clinical diagnosis, chronic diffuse nephritis, complicated of weakness and edema for six months; CO <sub>2</sub> combining power 32; admitted July 24, died July 29.
27. M. N.	June 30, 1916	46	M.	12.5	210	0	3 mos.	"	Patient admitted Apr. 2, last left hospital against advice May 15; condition slightly improved, reconstituted June 10; died July 2.
28. W. W.	Feb. 23, 1916	30	M.	12.5	76	0	5 mos.	"	Also fibrinoid phthiasis; admitted Feb. 7, discharged improved May 1; improvement coincident with rise in CO <sub>2</sub> combining power; returned to Ireland; died there in July.
29. W. S.	Jan. 30, 1917	...	M.	12.5	97	...	1 wk.	"	Patient brought to laboratory by clinic physician, who reconstituted at our prognosis; patient died a week later.
30. J. B.	Jan. 9, 1917	34	M.	12.5	110	3 to 10	11 mos.	"	Admitted Dec. 10, 1916; swelling of feet, hands and face one year; headache three weeks; heavy drinkers; discharged clinically improved June 9, with a urea N of 88.5 and a creatinine of 0.7 mg.; died Nov. 7, 1917.
31. J. M.	Sept. 11, 1918	38	M.	12.2	72	0	6 wks.	"	In hospital Aug. 29 to Sept. 28, reconstituted Oct. 2, died Oct. 14.
32. S. B.	Sept. 17, 1917	51	F.	11.6	57	0	1 wk.	"	Admitted complaining of acute gastritis Aug. 16, left hospital unimproved against advice Aug. 17, died shortly after being taken home.
33. F. E.	April 2, 1917	32	M.	11.5	102	0	1 wk.	"	Chronic diffuse nephritis and uremia; reconstituted Apr. 1.
34. M. O.	May 28, 1915	8	F.	11.1	90	0	6 wks.	"	Admitted May 11, double decapsulation of kidneys a May 13, died in uraemia June 20.

35. H. K.	July 27, 1915	41	M.	11.1	91	0 to 3	6 wks.	"	Admitted July 24; removed against advice Aug. 10; about two weeks later; mitral insufficiency; pleural effusion.
36. H. E.	Jan. 26, 1917	36	M.	11.1	139	4	1 wk.	"	Admitted Jan. 19; died Jan. 27, the day following this observation.
37. J. W.	April 14, 1915	34	M.	11.0	144	3 to 1	2 mos.	"	Slight cardiac hypertrophy; marked neuroretinitis; died April 16, two months after admission; showed marked clinical improvement, and said he felt perfectly well until three days before death.
38. A. D.	Oct. 13, 1916	30	M.	11.0	97	...	3 days	"	Clinical diagnosis, acute parenchymatous nephritis; admitted Oct. 13; died Oct. 16; CO <sub>2</sub> combining power 35 Oct. 13.
39. J. D.	July 16, 1915	33	M.	10.7	78	0 to 6	2 mos.	"	Admitted June 5; discharged improved July 17; died about two weeks later.
40. J. M.	Feb. 15, 1918	17	F.	10.2	307	0	1 wk.	"	Admitted Jan. 29; died eight days after this test Feb. 13; CO <sub>2</sub> combining power 30 Feb. 1.
41. C. G.	Sept. 24, 1915	26	F.	10.0	112	0	3 wks.	"	Malignant endocarditis with terminal uremia; admitted Sept. 7; died Sept. 24, the date of this examination.
42. J. G.	May 14, 1917	30	F.	9.8	62	0	7 mos.	"	In hospital Nov. 2 to Dec. 19, 1916, and Dec. 26 to Feb. 1, 1917; chief complaint on second admission, swelling of legs; 0 phthalein on Jan. 8; died at home June 1.
43. J. B.	Oct. 5, 1918	78	M.	9.8	60	Trace	2 mos.	"	Also hypertrophied prostate and cystitis; in hospital Sept. 28 to Oct. 29; CO <sub>2</sub> 31 Oct. 23; died Dec. 7 at home.
44. Z. F.	June 26, 1917	64	M.	9.7	70	12	5 mos.	"	Arteriosclerosis with hypertension, admitted June 11; discharged improved June 29; died about four months after leaving hospital.
45. P. L.	Mar. 7, 1918	30	M.	9.5	140	0	2 mos.	"	Admitted Feb. 28; also empyema; discharged improved Mar. 21; died about Apr. 22.
46. A. R.	June 21, 1918	51	F.	9.5	89	...	6 mos.	"	Outside patient; died Dec. 15.
47. J. S.	May 4, 1917	69	M.	9.4	89	...	2 wks.	"	Also prostatic obstruction; died about two weeks after this observation.
48. L.	July 21, 1916	..	M.	9.2	54	...	2 days	"	Private case outside hospital; syphilis; died on following day.
49. S. W.	Jan. 14, 1916	56	M.	9.1	224	0	2 wks.	"	Bacteremia, suppression of urine; lobar pneumonia; died two days after this observation.
50. I. H.	Nov. 16, 1917	43	F.	8.8	55	20-5	3 wks.	"	Admitted Oct. 26, complaining of pains in back and edema of feet; removed against advice Nov. 18; died two hours after leaving hospital.

TABLE I.—THE PROGNOSTIC VALUE OF THE CREATININE OF THE BLOOD IN NEPHRITIS—*continued*.

Case.	Date.	Age.	Sex.	Blood analyses.		Phthalein, two-hour output, per cent.	Time under observation.	Present condition.	Remarks.
				Creatinine, mg. to 100 c.c.	Urea N, to 100 c.c.				
51. V. A.	Feb. 15, 1916	27	M.	8.3	59	6-4-2	3 mos.	Dead	In hospital one week; died at home about three months later.
52. H. B.	Jan. 22, 1917	40	M.	8.3	75	...	1 yr.	"	Double polycystic kidney; admitted Jan. 22; nephrotomy on one side Jan. 24; left hospital improved, but died after an attack of pain on opposite side a year later.
53. J. W.	May 15, 1917	57	M.	8.2	95	...	2 wks.	"	Carcinoma of bladder; died in coma three days after this examination.
54. A. J.	Mar. 11, 1918	20	M.	8.0	131	...	5 days	"	Admitted Mar. 10; removed against advice Mar. 12; died three days later; possible bichloride poisoning.
55. J. S.	Nov. 23, 1914	50	M.	7.4	81	...	1 day	"	Slight edema of lower extremities; suppression of urine; died on day of admission.
56. R. W.	July 19, 1918	67	M.	7.1	82	0	3 mos.	"	Admitted July 18; blindness of right eye; shortness of breath for two years past; arteriosclerosis; retinal thrombosis; discharged improved Aug. 2; CO <sub>2</sub> 26 July 19 and 42 Aug. 2; died at home Oct. 11.
57. W. G.	July 13, 1914	8	M.	7.0	94	5	2 mos.	"	Acute nephritis of mixed type with uremia and edema; purpura hemorrhagica; died shortly after being removed from hospital against advice.
58. J. B.	May 3, 1918	46	M.	7.0	78	0	1 wk.	"	Died in coma six days after this analysis; at necropsy found hypertrophied heart and kidneys of arteriosclerotic type.
59. P. H.	June 28, 1918	64	M.	7.0	128	...	7 mos.	Unchanged	Clinical diagnosis, chronic parenchymatous nephritis and hypertrophied prostate; no operation; CO <sub>2</sub> on this date 45; in hospital June 21 to July 27; Jan. 27 condition unchanged although nitrogen retention had dropped; creatinine 4.4 and urea N 43.
60. O. P.	May 4, 1918	60	M.	6.9	97	...	2 wks.	Dead	Died apparently as a result of nephritic acidosis five days after this analysis; CO <sub>2</sub> Apr. 27, 32; operation for carcinoma of bladder four months previously; death not due to metastasis, as patient was not anæsthetic.



61. T. N.	Mar. 27, 1917	43	M.	6.8	105	0	2 mos.	"	Admitted Mar. 18 and removed against advice Mar. 30; previously in hospital but discharged Feb. 22; died shortly after being removed from hospital.
62. B. M.	June 26, 1918	47	M.	6.8	77	...	5 days	"	Acute nephritis; admitted June 22 and died June 27.
63. E. W.	Feb. 15, 1916	69	M.	6.7	104	...	2 wks.	"	Admitted Feb. 5; Wassermann positive; hypertrophied prostate; prostatectomy under novocaine; died Feb. 20.
64. E. H.	Aug. 14, 1917	20	F.	6.7	38	Trace	3 wks.	"	Double polycystic kidney; admitted Aug. 8; died Aug. 30, sixteen days after this observation.
65. J. H.	Feb. 7, 1917	61	M.	6.6	133	...	2 wks.	"	Admitted Jan. 24; died Feb. 8.
66. B. D.	July 18, 1918	70	M.	6.6	219	...	3 wks.	"	Admitted June 25; blood, June 27, creatinine 1.9 mg. and urea N 18; phthalein 85 per cent.; prostatectomy; patient did poorly for no apparent reason; died July 18.
67. S. G.	Nov. 8, 1917	53	M.	6.4	26	11-23	8 mos.	"	Admitted Oct. 20; discharged improved Dec. 7; very poor condition April 19, 1918; died in June.
68. F. A.	Sept. 5, 1916	53	M.	6.3	97	...	1 wk.	"	Clinical diagnosis, chronic diffuse nephritis; admitted Aug. 30; died Sept. 5.
69. J. McC.	Dec. 31, 1915	56	M.	6.2	53	2-8-7-10	8 mos.	"	Clinical diagnosis, chronic parenchymatous nephritis; admitted Dec. 27; discharged improved; CO <sub>2</sub> on admission 20; clinical improvement followed rise to normal; died from pneumonia Aug. 24.
70. C. L.	June 22, 1917	46	M.	6.2	39	23-10-26	5 wks.	"	Clinical diagnosis, chronic diffuse nephritis; uremia; admitted May 16; died June 24, two days after last blood examination.
71. B. S.	Oct. 18, 1918	52	M.	6.2	70	7 to Tr.	4 mos.	"	Chronic diffuse nephritis; marked edema at first; complained of headache and failing vision; carcinoma of sigmoid found at autopsy; in hospital Aug. 23 to Sept. 13 and Oct. 2 to Nov. 12.
72. A. F.	Feb. 18, 1916	45	M.	6.1	114	9	2 wks.	"	Multiple calculi of left kidney, nephrectomy, calculus of right kidney; nephrotomy; in hospital two weeks; died day after this observation.
73. N. W.	Nov. 20, 1916	21	F.	6.1	72	...	2 days	"	Also chronic polyarthritides deformans; sick four weeks; admitted Nov. 19; died next day.
74. F. F.	Dec. 18, 1917	8	M.	6.1	106	16-42-57	1 yr.	Recovered	Admitted Dec. 17 complaining of suppression of urine and edema of face; discharged improved Jan. 17; apparently recovered at present time.
75. J. C.	April 8, 1917	60	M.	6.1	41	10-7-9	21 mos.	Unchanged	Clinical diagnosis, chronic diffuse nephritis; admitted April 23; discharged improved June 10; readmitted a year later; Jan. 19, 1919, creatinine 4.3 mg. and urea N 64.

animals produces symptoms similar to those noted in uremia. Although Foster did not obtain sufficient of this compound to identify it, it is significant that guanidine compounds form very characteristic gold salts. These observations lend support to the view that the retention of creatinine may possess special significance in uremia. This topic is one upon which we are endeavoring to obtain further information.

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Of the remaining 12 cases showing over 5 mg. creatinine, Cases 74 to 85, 8 have died, 2 have apparently recovered, 1 is improved and 1 is unchanged. In view of our statement regarding creatinines of over 5 mg., it is of interest to examine the findings in these 4 cases. Case 74 (F. F.) suffered from acute suppression of urine, but with improvement in the activity of the kidneys the urea nitrogen dropped from 106 to 21 mg. in nine days and the creatinine from 6.1 to 4.2 mg. In Case 75 (J. C.) the creatinine maintained a level of over 5 mg. for not much more than a week, as shown in Table VI. It is interesting to note that a year later the blood presented quite a similar picture, although at this time the creatinine was 4.5 mg.

TABLE V.—INDIVIDUAL OBSERVATIONS ON CASE 74, F. F.

Date, 1917-1918.	Chemical blood analyses.				
	Creatinine. mg. to 100 c.c.	Urea N. mg. to 100 c.c.	Uric acid. mg. to 100 c.c.	Sugar, per cent.	CO <sub>2</sub> combining power, c.c. to 100.
Dec. 18 . .	6.1	106	11.4	0.106	54
21 . .	5.9	93	11.2	0.150	
27 . .	4.2	21	5.0	0.135	
Jan. 2 . .	4.0	23	...	0.096	
4 . .	3.7	26	...	0.090	
8 . .	3.8	28	...	0.122	
Oct. 30 . .	...	10			

Patient admitted to hospital on December 17 following suppression of urine for three days apparently due to an injury; convulsions, edema of face, vomiting four days, rapidly improved and left hospital on January 17; phthalein, December 19, 16 per cent.; December 24, 44 per cent.; December 26, 42 per cent. and January 4, 57 per cent.; apparently well at present time.

TABLE VI.—INDIVIDUAL OBSERVATIONS ON CASE 75, J. C.

Date, 1917.	Chemical blood analyses.				
	Creatinine. mg. to 100 c.c.	Urea N. mg. to 100 c.c.	Uric acid. mg. to 100 c.c.	Sugar, per cent.	CO <sub>2</sub> combining power, c.c. to 100.
April 24 . .	3.8	28	6.8	0.108	50
May 19 . .	2.1	35	7.4	0.120	
8 . .	6.1	41	5.5	0.132	
15 . .	5.2	30	7.7	0.126	
22 . .	3.3	28	7.7	0.120	
June 1 . .	3.1	36	10.4	0.117	
8 . .	4.5	26	...	0.129	
1918.					
April 2 . .	3.8	57	...	0.119	
26 . .	4.5	51	6.7	0.128	
1919.					34
Jan. 19 . .	4.3	64	...	0.135	

Patient in hospital from April 23 to June 10, 1916; phthalein 10 per cent. on April 25, 9 per cent. on May 3 and 7 per cent. on May 22; again in hospital April 1 to May 4, 1918, in rather poor health during October but feeling quite well in January, 1919.



With Case 79 (H. G.) the creatinine remained over 5 mg. for only a very brief period, probably not more than two or three days. A prostatectomy was performed upon Case 83 (R. McC.). On

TABLE VII.—INDIVIDUAL OBSERVATIONS ON CASE 78, H. G.

Date, 1917.	Chemical blood analyses.				
	Creatinine. mg. to 100 c.c.	Urea N. mg. to 100 c.c.	Uric acid. mg. to 100 c.c.	Sugar, per cent.	CO <sub>2</sub> combining power, c.c. to 100.
May 8 . .	4.9	45	9.0	0.140	46
15 . .	3.0	45	...	0.110	
18 . .	4.6	39	...	0.156	
22 . .	3.1	26	...	0.120	
25 . .	2.6	30	...	0.120	
29 . .	5.6	70	...	0.118	
June 1 . .	4.7	60	...	0.117	40
8 . .	3.5	48	...	0.120	
15 . .	2.5	23	...	0.129	
29 . .	3.8	31	...	0.141	
July 13 . .	3.2	26	...	0.120	

Patient admitted on May 2 complaining of pain in umbilical region, loss of weight, anorexia; no nephritic symptoms; phthalein on May 15, 35 per cent., May 18, 24 per cent.; left hospital improved on June 10; apparently well for more than a year past, in army at present time.

TABLE VIII.—INDIVIDUAL OBSERVATIONS ON CASES 94 AND 99.

Date, 1916.	Chemical blood analyses.				
	Creatinine. mg. to 100 c.c.	Urea N. mg. to 100 c.c.	Uric acid. mg. to 100 c.c.	Sugar, per cent.	CO <sub>2</sub> combining power, c.c. to 100.
		CASE 94,	M. MCA.		
Jan. 11 . .	3.6	41	4.6	0.110	22
25 . .	4.6	71	4.6	0.132	
April 11 . .	2.7	17	6.3	0.165	45
1917.					
May 9 . .	2.4	17	5.6	0.135	
		CASE 99, W. C.			
1916.					
Jan. 15 . .	3.5	44	9.5	...	22
17 . .	4.1	62	...	...	58
18 . .	2.0	42	5.6	0.152	56
19 . .	3.2	53	4.3	0.120	54
28 . .	1.9	19	2.5	0.138	
Feb. 1 . .	2.0	19	2.8	0.150	
1918.					
June 11 . .	1.8	16	4.4	0.150	

Case 94 admitted to hospital on January 7, also syphilitic; salivation as result of mercury salicylate given on January 16 and 18; phthalein on January 8, 14 per cent. on January 26, 30 per cent.; left hospital improved on February 3; apparently recovered judging from two subsequent blood examinations.

Case 99 admitted to hospital in coma apparently due to acidosis, obtained almost immediate relief with alkali therapy; use of alcohol important etiological factor; use of alcohol discontinued; perfectly well and blood essentially normal two and a half years later.

November 8, three weeks after the operation, the creatinine was 4.9 and the urea nitrogen 32 mg., essentially the same as on the first examination. One kidney had been removed at a previous operation. After two months the patient still appeared to be doing well clinically. Further discussion of the individual cases would appear to be unnecessary, although the findings on Cases 94 (M. McA.) and 99 (W. C.), may be of interest (Table VIII). These cases apparently completely recovered from the acute condition from which they suffered when admitted to the hospital. From an inspection of Table I it is apparent that the cases with the high creatinine values are for the most part clear-cut cases of interstitial nephritis, while many of the cases at the foot of the list suffered from various other complications.

TABLE IX.—OBSERVATIONS ON A CASE OF PARENCHYMATOUS NEPHRITIS.

Date, 1915-1916.	Chemical blood analyses.					Phthalein, 2-hour output, per cent.
	Creatinine, mg. to 100 c.c.	Urea N. mg. to 100 c.c.	Uric acid, mg. to 100 c.c.	Sugar, per cent.	CO <sub>2</sub> combin- ing power, c.c. to 100.	
Aug. 27 . .	1.9	28	2.3	0.18	...	8
29 . .	...	...	...	...	...	
31 . .	1.9	23	4.0	0.18	...	
Sept. 24 . .	3.0	25	3.3	0.17	...	24
Oct. 1 . .	2.9	25	2.5	0.14	...	
25 . .	...	...	...	...	...	
26 . .	3.0	29	2.8	0.14	...	
Nov. 11 . .	...	...	...	...	...	
19 . .	3.5	28	2.4	0.16	...	19
Dec. 3 . .	2.6	25	3.1	0.18	...	4
17 . .	2.8	21	...	0.18	...	
24 . .	3.6	27	3.0	0.18	54	
29 . .	...	...	...	...	56	
31 . .	...	...	...	...	...	
Feb. 18 . .	2.7	25	...	0.18	...	24
21 . .	...	...	...	...	...	
April 4 . .	3.0	28	3.4	0.18	...	
May 29 . .	3.4	46	8.3	0.15	...	

J. E. P. admitted on August 25, 1915, complaining of swelling of feet and abdomen and shortness of breath for eighteen months past; constant mild glycosuria of 0.5 per cent.; blood chlorides as NaCl on December 3, 0.73 per cent. and on February 18, 0.7 per cent.; died on June 1, 1916.

**GENERAL DISCUSSION.** The deductions which have been drawn regarding the blood creatinine apply particularly to cases of interstitial nephritis. In such conditions as bichloride poisoning and acute nephritis it is possible to have considerable nitrogen retention with ultimate recovery, for the reason that here the activity of the kidneys is only temporarily depressed. It is scarcely necessary to mention, however, that in comparison with chronic interstitial nephritis these cases are very much less common. In bichloride

poisoning it may be noted that Cohen and Bernhard<sup>29</sup> have reported a non-fatal case with a creatinine of 9.3 mg., while in a non-fatal case reported by Campbell<sup>30</sup> the creatinine reached 12.5 mg. Cases 74 and 78 in our series would naturally be classed as cases of acute nephritis.

The changes found in the blood in true cases of parenchymatous nephritis would appear to be quite different. Data on J. E. P., in Table IX, illustrate this point. As will be noted, no marked accumulation of creatinine ever occurred, and there was only a moderate retention of urea even up to the time of death. A detailed history of this case has already been published by Bailey in another connection.<sup>31</sup>

TABLE X.—CASES WITH MARKED UREA RETENTION BUT WITH ESSENTIALLY NORMAL CREATININE VALUES, ALL IMPROVED.

Case.	Date.	Age.	Sex.	Blood analyses.		Phthalein 2-hour output, per cent.	Remarks.
				Creatinine. mg. to 100 c.c.	Urea N.		
1. J. P.	April 23, 1915	34	M.	3.2	72	17	Acute parenchymatous nephritis with edema of extremities and difficult urination, remained in hospital 42 days after this date.
2. L. B.	Aug. 6, 1915	32	F.	3.1	67	..	Pulmonary tuberculosis and acute parenchymatous nephritis; in hospital 92 days.
3. D. B.	Oct. 9, 1917	38	M.	3.1	65	50	Tabes dorsalis and acute nephritis, after week's rest urea N dropped to 15 and phthalein rose to 68.
4. K. K.	Dec. 29, 1916	46	F.	3.4	63	..	Nephrolithiasis, nephrotomy under spinal anesthesia.
5. M. C.	July 18, 1916	11	M.	2.8	60	18	Acute parenchymatous nephritis with generalized edema, in hospital one month.
6. A. M.	July 7, 1916	63	M.	2.3	51	26	Endocarditis and syphilitic aortitis, edema of extremities and dyspnea; in hospital one month.
7. B. S.	Jan. 2, 1918	70	M.	2.6	50	10	Chronic parenchymatous nephritis; left hospital 30 days after this date.
8. M. S.	Dec. 12, 1916	35	M.	2.2	50	..	Duodenal ulcer, alcoholic history; 2 days before leaving hospital phthalein 57 per cent.
9. H. P.	Mar. 5, 1918	32	M.	2.4	50	..	Pleural effusions; tuberculous kidney removed 1 year ago.
10. R. K.	Feb. 2, 1918	11	F.	2.5	50	..	Acute uremia, anuria; after 3 days phthalein 32 per cent.

Inasmuch as the blood urea and the phenolsulphonephthalein test on the urine are likewise recorded in parallel columns in Table I, it affords an opportunity to compare the value of these three tests. As pointed out in the introductory portion of the paper the blood

<sup>29</sup> Jour. Am. Med. Assn., 1917, lxi, 440.

<sup>30</sup> Arch. Int. Med., 1917, xx, 919.

<sup>31</sup> Bailey: AM. JOUR. MED. SC., 1919, clvii, 221.

urea is subject to much greater fluctuation than the creatinine, due largely to the difference in its origin. Since the urea is a more sensitive indicator of renal impairment it is particularly useful as a diagnostic test in medical cases<sup>32</sup> or as a pre-operative prognostic test in surgical cases,<sup>33</sup> but much less valuable than the creatinine as a prognostic test in cases of advanced nephritis. That a considerable accumulation of urea may occur without a retention of creatinine, but with ultimate improvement in the condition of the patient, is evident from the data presented in Table X. An accumulation of non-protein and urea nitrogen occurs in acute intestinal obstruction,<sup>34</sup> but an accumulation of creatinine should not occur unless the kidneys are involved. All these facts lead to the conclusion that the accumulation of urea possesses a somewhat different significance from that of creatinine.

The results on the phthalein test recorded in Table I speak well for the prognostic value of this test. They agree excellently with the creatinine in the prognosis indicated, and in one or two instances the information appears to have been especially significant. Case 30 is the most notable illustration. Here there was an appreciable output of phthalein for some time, and the case survived much longer than any other with a similar creatinine retention. As has been pointed out by Frothingham, Fitz, Folin and Denis,<sup>35</sup> however, there is this difference between the phthalein and the blood tests: The phthalein test shows the renal function at the moment, while the blood tests (they used the non-protein and urea nitrogen) are rather a measure of the accumulating difference between the amounts of waste nitrogen produced in metabolism and the amounts eliminated by the kidney. In an acute condition a negative phthalein might be encountered without a marked creatinine retention. In advanced cases of nephritis, on the other hand, changes in condition are accompanied by changes in the blood creatinine, but obviously there can be no change in a negative phthalein. The blood creatinine and urea and the phthalein test excellently supplement each other in indicating the extent and type of impairment of renal function, and where possible, use should be made of all three tests. From the standpoint of prognosis, however, we believe the creatinine gives the most reliable information, and in cases beyond medical help, such as the majority of those listed in Table I, this is the factor of greatest importance.

Data on the presence of protein and casts in the urine of the cases in Table I have been intentionally omitted. In passing, it should perhaps be noted that several of the very severe cases failed to show either protein or casts in the urine.

<sup>32</sup> Kast and Wardell: *Arch. Int. Med.*, 1918, xxii, 581.

<sup>33</sup> Squier and Myers: *Jour. Urol.*, 1918, ii, 1.

<sup>34</sup> Tileston and Comfort: *Arch. Int. Med.*, 1914, xiv, 621; Whipple and Van Slyke: *Jour. Exper. Med.*, 1918, xxviii, 213.

<sup>35</sup> *Arch. Int. Med.*, 1913, xii, 245.

**SUMMARY.** Observations are recorded on 100 cases of nephritis showing creatinine retention. Of these 100 cases, 85 had a creatinine of over 5 mg. per 100 c.c. of blood, the figures ranging from 5.1 to 33.3 mg.; 80 of these 85 cases have died. Of the 5 remaining the condition of 3 is essentially unchanged, while 2 have recovered. These 2 cases showed only a temporary elevation of the blood creatinine.

A considerable number of the 85 cases were able to be up and about and some showed decided clinical improvement. The creatinine gave us a better prognostic insight into these cases than either the blood urea or phthalein tests, which were made simultaneously. It is our opinion that in advanced cases of nephritis the blood creatinine furnishes a more reliable prognosis than any other test we possess.

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### REMARKS ON OCULOGYRATION AND ON THE LESION CAUSING COMPLETE BILATERAL OPHTHALMOPLÉGIA.<sup>1</sup>

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FRENCH neurologists employ the term *oculogyre* and its various modifications. In seeking English equivalents for these terms I have consulted the *Standard Dictionary*, as I am informed by certain ophthalmologists with whom I have conferred that the French usage is not common in American ophthalmology. A gyre may mean a gyration, it may also mean a gyrus, as one of the convolutions of the brain. Gyration means: "The act of turning, as a body on its axis of rotation, while simultaneously whirling about an axis of revolution," and it seems better adapted to the translation than gyre. I have employed the terms dextrogyration and sinistrogyration to mean right lateral associated movement of the eyeballs and left lateral associated movement, respectively.

The attempt is made in this paper to discuss certain aspects of oculogyration and to distinguish clinically between lesions above and below the nucleus of the branch of the oculomotor nerve supplying the internal rectus muscle, causing disturbance of lateral associated ocular movement; also to explain the lesion causing complete bilateral ophthalmoplegia in a way I have not seen employed in literature. A lesion at a considerable distance above the oculomotor nucleus probably could not cause persistent paralysis of ocular movements, as such movements are bilaterally represented in the cerebral cortex.

G. S., aged fifty-two years, was admitted to the University Hos-

<sup>1</sup> Read before the Philadelphia Neurological Society, February 28, 1919.

pital December 8, 1918. He used alcohol in moderation. The downward and inward rotation of the right eyeball from the action of the superior oblique was distinct when he came to the hospital, on December 8, 1918. External rotation of the right eyeball was preserved, but there was complete right oculomotor palsy. An examination revealed nothing of importance in addition to the ocular condition. His gait and tendon reflexes were normal. The Wassermann test of the blood was negative; a spinal puncture gave 8 c.c. of fluid; the cell count was 11 cells per cubic millimeter; the pressure of the spinal fluid was slightly elevated; the Wassermann and globulin tests of the fluid were negative.

He brought the following note from Dr. Alfred Cramer: "When I first saw you on November 11, 1918, you told me that your eyes had given you trouble for only two weeks previously. You complained chiefly of seeing double, though your general health had been below par for some time. I doubt if you had influenza at the beginning of your trouble. My examination showed there was a palsy of the superior rectus muscle of the right eye and a partial drooping of the right eyelid. The rotation of the eyeballs was good in other directions. The state of your candle field with a red glass before the left eye showed there was diplopia in the primary position, the red candle showing below and slightly to the left-hand side. As the candle was moved down toward the lower field the candle flames came nearer and nearer together until they apparently fused. Neither flame seemed to be oblique, except in rotation up and to the right.

"The condition remained about the same until November 29, but during the week since this date there has been considerable change. I now find there is a complete paralysis of all the muscles of the right eye, with the exception of the external rectus muscle and superior oblique. There is also inability to lift the right upper eyelid. There also seems to be a slight limitation of the upward rotation of the left eyeball. There is, too, a paralysis of the iris, the pupil being immobile and partially dilated. So far as I can see there are no changes in either eye-ground. The vision in each eye is practically normal without glasses. Negative Wassermann."

Notwithstanding the negative findings the man was treated as a possible syphilitic, and on December 15, seven days after admission to the hospital, some improvement in the oculomotor palsy of the right eye was noticed, and this improvement continued; but it was soon observed that he had no rotation of the right eye to the right of the midline. Dr. J. T. Carpenter confirmed this observation on December 27, and also reported that the eye-grounds showed no specific lesions and both disks showed clear edges and there was no swelling. Soon after this it was observed that the left internal rectus was very weak.

At the present time the complete right oculomotor palsy has

changed considerably; he now has some inward and downward movement of the right eye; no ptosis of the upper lid, but complete paralysis of associated upward movement of the eyeballs and nearly complete paralysis of dextrogyration of the eyeballs and partial palsy of sinistrogyration; nor does the left internal rectus function as well in convergence as in dextrogyration. The downward motion of the left eye is normal or nearly normal.

At the time the right oculomotor palsy was complete, Dr. Cramer found, December 6, 1918, a slight limitation of the upward rotation of the left eyeball. The gradual but pronounced improvement of the motion of the right eye was associated with a nearly complete paralysis of outward motion of the right eye and of upward motion of the left eye. It might be thought that this external rectus palsy was produced by the use of arsenobenzol, but the additional palsy of the left internal rectus made the palsy an associated one, which could hardly be caused by this drug.

Paralysis of upward associated movement, as I<sup>2</sup> have shown by previous observations, indicates a lesion near the corpora quadrigemina. There is evidently a lesion in this man in or near the corpora quadrigemina, causing paralysis of upward associated movement, marked paralysis but not complete of dextrogyration and slighter paralysis of sinistrogyration; and yet he presents no incoördination of the limbs, as one might expect, from disorder of the superior cerebellar peduncles. The lesion cannot be large enough to cause implication of these structures.

Were his condition associated with hemiplegia the symptom-complex would be what the French writers call the syndrome of Foville, and such a case was reported recently by André Leri and Perpère.<sup>3</sup>

A case of paralysis of oculoxyration on the side opposite to the hemiplegia was reported by Dr. Potts and myself from a tubercle of the pons,<sup>4</sup> and this heterolateral paralysis is indicative of a lesion of the pons; for example, paralysis of dextrogyration with eyes turned to the left associated with left hemiplegia indicates a lesion of the right side of the pons. It means that a lesion of the connecting fibers of the nucleus of the nerve to the internal rectus of one eye with the nucleus of the opposite abducens nerve has occurred, and usually near the abducens nucleus. In this form the function of the affected internal rectus muscle may be preserved in convergence, indicating that the nucleus of the nerve to this internal rectus and its cortical connection cannot be destroyed.

I believe that when the central pathway of corticonuclear oculoxyration is paralyzed above or in the nucleus of the nerve to the

<sup>2</sup> Jour. Nerv. and Ment. Dis., 1905, and Obersteiner's Arbeiten, vols. xv and xvi.

<sup>3</sup> Rev. Neur., May-June, 1918, 530.

<sup>4</sup> Univ. of Penna. Med. Bull., December, 1903.

affected internal rectus the function of this muscle in convergence will disappear or become much impaired, as it did in the case I now report. When the break occurs in these fibers above this nucleus no impulses can pass into this nucleus for either form of function of the internal rectus, *i. e.*, for oculogyration or for convergence; but when the break occurs in the posterior longitudinal bundle, and therefore below the nucleus of the nerve to the internal rectus, the function of the internal rectus muscle in convergence may be preserved, as it has no relation to the abducens nerve, but oculogyration demanding the function of this muscle in association with the function of the heterolateral external rectus will be lost. So far as I know this diagnostic distinction of a lesion above the nucleus of the nerve to the internal rectus as compared with one in the posterior longitudinal bundle below this nucleus as of value in localization, has not been described, and it applies to the lesion above the nucleus only when it is near the nucleus.

As the patient under discussion has paralysis of upward associated movement with paralysis of dextrogyration and paresis of sinistrogyration, and still less power of the left internal rectus in convergence than in the associated movement of this muscle with the right external rectus, he probably has a lesion of the corpora quadrigemina, and not one on the base involving the nerves at their exit.

It is not necessary to assume that the paralysis of the right external rectus muscle in this case is caused by a lesion of the abducens nerve or its nucleus. Complete ophthalmoplegia implicating all the nerves supplying the eyeballs has been explained usually as the result of inflammatory lesions of all the ocular nuclei, but this explanation, when all other cranial nerves entirely escape, has seemed to me unsatisfactory, especially as bilateral complete ophthalmoplegia has been repeatedly observed without other nerve lesions. I believe that when a lesion destroys the nuclei of the trochlearis and oculomotorius nerves bilaterally, which a comparatively small lesion may readily do, as these nuclei are very near together, it must destroy the connections in the posterior longitudinal bundles between the nuclei of the internal recti and those of the external recti, and consequently paralysis of the external recti muscles will result without any lesion of the abducens nerves or their nuclei. The movements of the two eyeballs are intimately associated and a lesion of the central pathway of corticonuclear oculogyration near the nuclei affects the movements of both eyeballs.

Dr. T. B. Holloway made the following report, April 16, 1919:

Your patient was seen by me April 15, and I found that since his last observation the vision of his left eye had deteriorated considerably and is now but 3/150. The other conditions were as follows:



The veins of the upper lid of the left eye are more prominent than those of the right. There is a ptosis of the left upper lid, the palpebral fissure measuring 6 mm. in contrast to 10.5 mm. for the fellow eye. The left eye is distinctly proptosed and displaced downward 2.5 mm. and outward 1 mm. Hertel's exophthalmometer shows the apex of the left cornea to be 3.5 mm. more than the right. There is decided resistance to backward displacement of the globe. No visible or palpable pulsation is present. I did not have a stethoscope to listen for a bruit. Palpation of the anterior portion of the orbit reveals a distinct fullness at the upper and inner angle. The caruncle and plica are reddened and prominent.

Upon rotation of the globes to the right there is a decided restriction of movements, the right eye rotating outward and the left inward not more than 10 degrees. Upon rotation to the left the left eye rotates to within 2 mm. of the external canthus, while the rotation inward of the right eye is hardly as great. The upward rotation is restricted in both eyes, but distinctly more so in the left. There is slight downward restriction of both eyes. Upon attempts to converge, the left eye practically fails and soon deviates outward.

The right pupil measures 4.5 mm., is distinctly eccentric and is displaced upward and slightly inward; the position of the left pupil is normal and it measures 3 mm. There is no direct or indirect pupillary light reflex in the right eye, but in the left there is a slight direct and greater indirect light reflex. Both pupils react slightly upon attempts at convergence and accommodation.

The media are clear, the disks are not pathological and there are no fundus changes aside from slight increase of the arterial reflex and some venous pressure signs, due to incipient sclerosis of the vessels.

In the left eye the retinal veins appear to be a trifle fuller and darker than in the right.

The field of the right eye does not show any changes for form or colors, while that of the left shows a cut across the upper portion of the form field, to about 25 degrees, that seems to be more than would be accounted for by the ptosis. With the left eye he could not notice any colors in a 10 mm. circle.

**A CASE OF DIABETES MELLITUS WITH SYPHILIS.**

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IN the summer of 1918 a special diabetic service was established in this general hospital, under the direction of Capt. Frederick M. Allen, for receiving cases of diabetes developing among the military and naval forces. The case described below was observed while the writer was acting as ward surgeon on this service, and is presented on account of points of diagnostic and therapeutic interest in connection with the complicating or causative factor, syphilis.

**CASE HISTORY.** Lieut., U. S. N. R. F., aged forty-three years, American ancestry. Family history is negative except for obesity, which was absent in the father, moderate in the mother and also in the five brothers in about the same degree as in himself. Height of patient, 5 feet 8 inches; maximum weight, 196 pounds. He has had no known infections except mumps and diphtheria in childhood. Married twelve years; one healthy child, aged eleven years; not obese; no miscarriages by wife. The patient has seen tropical service for several years as engineer of steamers in the West Indian trade; no tropical diseases known. Venereal infection is positively denied and no suggestive symptoms elicited on careful questioning.

**Present Illness.** December 18, 1917, on board ship, the patient suffered a definite acute onset of weakness, loss of weight, general malaise, polyuria, polydipsia and loss of appetite, so that he ate chiefly fruit for several days before reaching port. There his family physician diagnosed diabetes and acute pancreatitis, and subsequently, in view of the later developments, sent word through the patient to emphasize the latter diagnosis; grounds for making it not learned. An eleven-day fast was imposed, glycosuria ceasing on the ninth or tenth day. Graduated diets were instituted, following the Hill and Eckman manual. After three months the patient was able to resume duties as engineer, at a weight of 150 pounds. He now felt entirely well, was able to follow diet on shipboard, and remained free from glycosuria.

June 2, 1918, his vessel was torpedoed, and he was exposed to cold and hunger in an open boat for forty-six hours. On reaching land he received the same high diet given the other survivors, and intense diabetic symptoms promptly returned. He arrived home in a serious state of weakness, and the same physician resumed treatment, with fasting, low diet and sodium bicarbonate. Enlargement of the liver was now found and marked ascites rapidly developed. Treatment was entirely unsuccessful, because the ascites and some general edema were taken to indicate that the patient was too weak

to bear fasting. Drugs, such as digitalis, pituitrin and increasing doses of sodium bicarbonate, were tried in vain. Accordingly, more or less glycosuria and acidosis were allowed to continue on a restricted diet, and an early fatal outcome was anticipated.

The patient was admitted to this general hospital in this condition, September 5, 1918. Weight 130 pounds, with a combination of slight general edema and a large ascites which distended the abdomen to the maximum. Careful examinations were made by various members of the medical and surgical staffs, with results negative except as follows: complexion, slightly yellow and also dusky, especially on the exposed surfaces, said to be due to exposure to weather. No jaundice or pigment patches on the skin or mucous membranes. Special sense organs, normal. Nervous system: knee-jerks absent or feebly present; marked myotonia reaction; no lumbar puncture performed. Thyroid and heart normal, also glandular system, except small palpable inguinal nodes. Lungs clear, but both pleural cavities contained movable fluid up to the sixth rib posterior, encroaching seriously on the aeration space of the lungs and pushing the heart upward. The left lobe of the liver was plainly palpable through the thin abdominal wall, moderately firm, smooth or very slightly nodular on the surface, and entirely free from pain or tenderness. The fairly sharp edge descended to about 5 cm. above the umbilicus and passed upward under the left costal margin in the left mammary line. No enlargement of the right lobe was demonstrable. It was impossible to investigate the other abdominal viscera on account of the ascites.

Laboratory reports were received as follows: Plasma sugar, 0.400 per cent.;  $\text{CO}_2$  combining power 75.8 volume per cent. Blood count: hemoglobin, 56 per cent.; red blood cells, 4,130,000; leukocytes, 7400. Differential count: small mononuclears, 56 per cent.; large mononuclears, 9 per cent.; transitional, 4 per cent.; polymorphonuclears, 31 per cent.; Wassermann negative.

It was immediately obvious that the condition was diabetes of considerable severity, accompanied by a slight bicarbonate or salt edema, and ascites due to some unknown abdominal cause, the chief suspicion pointing to the liver. The explanation of the hydrothorax also probably lay in one or the other of the above-mentioned conditions.

Treatment was begun accordingly by fasting, mitigated with clear soup, coffee and bran muffins, omitting both sodium bicarbonate and sodium chloride. The fast was well borne, glycosuria clearing on the sixth day, while ketonuria continued for fourteen days. The general edema promptly cleared and the hydrothorax gradually lessened, but the ascites remained practically unchanged. The patient was now given a diet consisting of protein 40 grams and carbohydrate 10 grams, fat being excluded. The protein intake was later advanced to 60 grams and fast-days were interpolated fre-

quently. After one month of such treatment the plasma sugar remained in the neighborhood of 0.200 per cent. The patient improved in strength and spirits, but experienced considerable difficulty in walking on account of the heavy, distended abdomen. The fluid in the chest had entirely cleared at this point. A barium series was taken, the radiogram failing to locate any abnormality. Paracentesis abdominis was performed, four liters of clear amber-colored fluid being withdrawn and about an equal quantity left, because of threatened collapse. The laboratory report on the ascitic fluid was as follows: specific gravity, 1020; cell count, 1760 per cm. Differential count: red cells, 9 per cent.; polymorphonuclears, 27 per cent.; small mononuclears, 38 per cent.; large mononuclears, 19 per cent.; transitionals, 9 per cent.; bile reaction negative. Guinea-pig injection was negative for tuberculosis. The fluid rapidly reaccumulated and the abdominal distention again reached the maximum.

From October 1 to December 11 a low protein-fat diet was given, strictly carbohydrate-free, the daily intake never exceeding 1500 calories. There was an occasional trace of sugar in the urine and the plasma sugar remained persistently high. The diagnosis of the unknown abdominal condition meantime called for consideration of various possibilities, including cancer, peritoneal tuberculosis, with or without Addison's disease, syphilis, hemochromatosis, simple hypertrophic cirrhosis, hepatic cyst, etc.

December 11, 1918, a second paracentesis was performed and about six liters of clear amber fluid withdrawn. Wassermann on the fluid was two plus (army nomenclature), other findings not varying from the previous report. The entire abdomen was now easily palpated and the only abnormality noted by several observers was the asymmetrical enlargement of the left lobe of the liver. A provocative dose of salvarsan was administered and after three days the blood Wassermann was one plus (army nomenclature). The patient was placed on very active treatment, with potassium iodide and mercury pushed rapidly to tolerance. The diet during this *régime*, December 20 to January 20, was cut to 60 grams of protein and fat enough to make 600 calories, carbohydrate-free. The left lobe of the liver steadily diminished to 3 cm. below the xiphoid cartilage and the ascites mostly disappeared, no further paracentesis being necessary.

At present the patient is in good spirits and fair state of nutrition, despite the long and rigid dietary *régime*. The therapy resolves itself into two distinct lines. The low-calory protein-fat diet has been continued to the present, and it is noteworthy that the blood sugar is now approaching the normal (0.12 per cent., February 2, 1919) for the first time following five months of strict dietary regulation and one and a half months of antiluetic treatment.

Two lessons may be pointed out from the experience with this case:

(1) though probably diabetes is relatively infrequently due to syphilis, search for this cause, whether inherited or acquired, should be carefully made by all possible means, and merely a negative Wassermann reaction in the blood should not be accepted as excluding it; (2) diabetes, particularly in the advanced stage, may not be (and probably as a rule is not) perceptibly altered by antiluetic treatment. This is logical from the fact that syphilis here presumably produced fibrous changes in the pancreas just as it did in the liver. What can be hoped from such therapy is the checking of further advance of the infectious process, not the repair of existing damage and the improvement of the diabetes. Such cases stand practically on the same plane as diabetes from other causes, and the same dietary control is necessary. It will be noted that the diabetes in this case is of marked severity, as shown by the minimal tolerance acquired in long treatment. The patient has been benefited in respect to strength, comfort and presumably longevity, but the ultimate outcome in view of the advanced conditions present is dubious.

## REVIEWS

ANATOMY OF THE HUMAN BODY. By HENRY GRAY, F.R.S.  
Twentieth Edition, thoroughly revised and reëdited by WARREN  
H. LEWIS, Professor of Physiological Anatomy, Johns Hopkins  
University, Baltimore. Pp. 1396; 1247 illustrations. Phila-  
delphia and New York: Lea & Febiger.

WHEN a medical book runs into twenty editions in sixty years it must have an unusual hold on the confidence of the medical world. When seekers after anatomical guidance still turn with assurance to the pages of *Gray*, one must conclude that it fulfils its particular purpose with success, and this impels one to inquire, What are the distinctive merits of the work? That it is something inherent in the work itself is evident from a comparison of the latest edition with the first edition and with intervening issues. The result of the survey is that the newest edition has retained the outstanding features of its predecessors. One omits from such positive judgment the edition in Chinese, translated by Dauphin W. Osgood and published at Foochow for the American Missionary Board in 1881. On opening the book the first thing one encounters is the end of the anatomical vocabulary in English and Chinese, and on the last leaf is the title-page. But even here one catches sight of some of the familiar illustrations, though the attached legends are in Chinese. In the original publication, issued in 1858, there were 750 pages, with 363 illustrations. The text was by Henry Gray and the illustrations by H. V. Carter, both of St. George's Hospital Medical School, London, and the dissections jointly by Gray and Carter. Both names appear on the title-page, and it would seem only just that both names should still appear, for if one compares the book with the other student anatomies of the day it is certainly the illustrations which mark the most definite improvement over the contemporary books. The *Dublin Dissector*, the *London Dissector* and *Horner's Anatomy and Histology* were small volumes, with few or no illustrations. The same was true also of Quain's and of Paxton's *Anatomy*, of which an American edition was edited by Winslow Lewis, Jr., demonstrator of anatomy in the medical department of Harvard University. Gray and Carter, however, used a larger size of page and put the illustrations in ample form. A whole page, for instance, was devoted to the bones of the hand, and throughout space was liberally bestowed upon the figures. This is the modern note in a book designed especially for student

use. Without detracting from the value of the descriptive part, one can safely say that the illustrations by Carter, reproduced in clear form, are the distinctive improvement on the student anatomies of the middle of the nineteenth century. Since the first edition many able anatomists have acted in an editorial capacity, but as the present editor says in the preface, "Much of the original text persists." One gains an idea of how much surveying has been done if one consults the title-page of the "new American edition from the tenth English edition" of 1883. After mentioning that the text was by Gray, it proceeds: "With an introduction on general anatomy and development by T. Holmes, drawings by H. V. Carter, with additional drawings (by Dr. Westmacott), edited by T. Pickering Pick; with new sections on landmarks, medical and surgical, by Luther Holden, with additions by W. W. Keen." In later editions other names replace some of these, and now in this the twentieth edition only Gray and the present American editor, Warren H. Lewis, are mentioned. But one can readily see what a succession of clever scientific men have used their energies in molding the book into its present form. The present editor has made several additions and alterations. New matter has been added on laws of bone architecture, mechanics and variations of muscles and short lists of important references to literature are given at the end of the chapters. The sections on ductless glands, central nervous system and sympathetic nervous system have been partly rewritten. Under its new editorship the book will no doubt continue to receive its due share of patronage, along with the several other excellent student anatomies which are now available. Some of these are more complete in certain respects, as in the consideration of microscopic structure and embryology. But for ready reference to structures connected with the gross relations the present volume is excellent. The text is a model of simplicity, the descriptions are not too long, the illustrations are clear, some think even too diagrammatic, and everything is tabulated. This method of presentation may give the impression of a greater rigidity of form than is always adhered to by Nature, but for gathering together many details into a learnable form the method still has its place.

W. H. F. A.

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THE SURGERY OF ORAL DISEASES AND MALFORMATIONS. By GEORGE VAN INGEN BROWN, D.D.S., Oral Surgeon to St. Mary's Hospital, Milwaukee. Third edition. Pp. 703; 590 illustrations. Philadelphia and New York: Lea & Febiger.

THE preparation of a satisfactory book on oral surgery presents unusual difficulties, in that most of the surgical conditions which must be taken up are general in their nature and familiar to most

surgeons. They are discussed in every good text-book on general surgery. Thus we find here much space given over to such general subjects as anesthesia, hemorrhage, shock, infections, diseases of bones and glands and to tumors. But the author properly notes that the oral surgeon comes into contact with dentists, general surgeons, internists and the various other specialists. His aim has been to produce a volume which will be a book of reference touching all these medical interests in their oral relations. After excluding all those portions dealing with general conditions with which surgeons and general practitioners are familiar, there still remains a sufficient amount of important special oral surgical matter to make the book distinctly worth while to those who have need of knowing something of this field. There are 20 good colored plates, most of them with two and some of them with three illustrations on a plate. These cover well the important conditions peculiar to or common in the mouth and surrounding parts. The two illustrations on Ludwig's angina, however, are deserving of criticism. One of them, Fig. 87, was taken from a paper by the reviewer with due credit, but rather carelessly. It is said to show the ulcerated condition in the floor of the mouth and other parts (in Ludwig's angina). It was intended in the original paper to show the normal anatomy of the floor of the mouth with the tongue removed and had lines pointing to the structures of particular interest. The other illustration, Fig. 88, is said to show the "characteristic position of the head (in Ludwig's angina) in the effort of respiration," but it does not. This is, however, a small matter in view of the great number and wide variety of conditions included in a treatise on a specialty of such a limited field.

T. T. T.

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THE DISEASES OF INFANCY AND CHILDHOOD. By HENRY KOPLIK, M.D., Attending Pediatrist to the Mount Sinai Hospital; Consulting Physician to the Hospital for Deformities; Ex-President of the American Pediatric Society. Pp. 928; 239 engravings. Fourth edition. Philadelphia and New York: Lea & Febiger.

THE earlier editions of this well-known work are to be found in every pediatrist's library, a fact that testifies to its worth more than can any review. This fourth edition, however, has been brought abreast of the learning of today, and much therefore that is new has been incorporated in this volume. The chapters on acidosis, on infant feeding, on the infectious diseases and on diseases of the blood and circulatory system particularly have been revised and added to. The most important part of a book on diseases of infancy is, of course, that part that deals with infant feeding. Dr. Koplik has clearly set forth the underlying principles that are guides in this



phase of pediatrics, and using the top-milk method describes fully the modification of cow's milk for infant feeding. While it might be said that top-milk feeding will not always prove practical or economical in dispensary practice or among the poor where ignorance and cost have to be borne in mind, to meet the indications that the author has so exceptionally well pointed out, top-milk feeding is necessary. Moreover, it keeps in the mind of the physician the percentages he is using, a necessity that cannot be too emphatically insisted upon. The feeding beyond the first year has been carefully planned in this volume, and is worthy of careful reading. So little attention is sometimes given to the diet necessary to full development and health of the run-about child.

Congenital anomalies and diseases of the newborn, disturbances of nutrition and infectious diseases are well considered and of particular value to the practitioner is the completeness of detail given in connection with treatment. It is of further value in that reference can be found to many of the unusual conditions and diseases of infancy and childhood not mentioned in the books of similar character.

It is fitting in this instance to give praise to the publishers for the unusual attractiveness of the book and its arrangement. The plates and engravings are new and are taken from actual cases of the author, and exceptionally well illustrate the text. C. N. S.

THE SCHOOL CHILDREN OF ENGLAND. The Annual Report for 1917 of the Chief Medical Officer of the Board of Education of Great Britain. London.

THE last, 1917, annual report of Dr. George Newman, the chief medical officer of the Great Britain Board of Education, has as usual much of interest for us. Two sections are especially worthy of comment. The first is the discussion of the effects of war on the children in the schools. The difficulty in keeping up the School Medical Service because of the depletion of the staff of medical men and nurses and the evil effect of child employment and the occupation of mothers in industry are mentioned. The greatest apprehension, however, was felt by school medical officers that the health of children would suffer from certain conditions arising from the war. These conditions were the food rationing, especially the restriction of fat and sugar, the high price of food, the lessening of parental control, daylight saving and air raids. In regard to food, Dr. Newman reports that more or less general inquiries have been made, and that, so far as the school children are concerned, there is little evidence of serious injury.

In London, the percentage of children found in poorly nourished

condition in the third term of 1917 was considerably less than half the percentage found in 1913, the year before the war.

"The progressive reduction in the number of the children found with poor nutrition has been maintained," writes Dr. Hamer, the Medical Officer for London, "the figures in this respect being better for 1917 than 1916, and for leavers less than half the pre-war figures. It is noteworthy that this reduction has been continued right up to the end of 1917, and that the figures for the third term of that year are the best in this respect that have ever been attained. On the other hand, the percentage of children returned as of good nutrition as opposed to fair nutrition only, has shown diminution. This is no doubt to be explained by the anxiety of many parents to fall in with the voluntary rationing schemes suggested by the Food Controller."

Year.	Intermediate.					
	Boys.			Girls.		
	Good.	Fair.	Poor.	Good.	Fair.	Poor.
1913	22.0	62.2	15.8	25.1	61.4	13.5
1914	19.9	70.1	10.0	22.8	68.2	9.0
1915	21.1	69.8	9.1	23.3	69.0	7.7
1916	23.6	67.0	9.4	26.4	65.6	8.0
1917	20.9	70.6	8.5	22.3	70.2	7.5

Year.	Leavers.					
	Boys.			Girls.		
	Good.	Fair.	Poor.	Good.	Fair.	Poor.
1913	26.4	58.9	14.7	30.6	55.1	14.3
1914	26.4	61.1	12.5	29.9	58.6	11.5
1915	29.0	63.8	7.2	32.8	60.9	6.3
1916	29.4	63.8	6.8	31.4	62.3	6.3
1917	27.1	66.7	6.2	28.5	65.2	6.3

The consensus of opinion is that the school children are generally in a better nourished condition than before the war. One deleterious result of war seems to be a general increase in uncleanness among children, especially in the percentage in verminous heads and bodies. This is attributed to lack of parental supervision and partly to the introduction of infection from returning troops.

Air raids apparently had slight if any effect on the nervous complaints of school children in London.

The effect of the Daylight Saving Act in some areas resulted in depriving children of an hour of sleep, though the complaints in the second year of its operation were greatly reduced.

There seems little doubt that the wonderful result of checking growing malnutrition in London school children in the midst of war conditions was due largely to the provisions of the Education (Provision of Meals) Act, 1906, and the amending Act of 1914, which enabled the Local Education Authority to feed any children in the public elementary schools, even on holidays and on other days when the school is not open. These meals may be given free of charge, or parents and guardians may be made to pay, and the Exchequer provides a grant-in-aid not exceeding one-half of the expenditure approved. The number of necessitous children fed under the provisions of the Act reached a maximum in 1914, of 422,401, with a total of 29,560,316 meals in the year 1914-1915.

With the distribution of separation allowances and the rise in wages, the number of necessitous children being fed fell until, in 1917-18, it was less than that at any other period since 1906. A large number of children whose parents or guardians were able to pay all or something for these meals were being fed in 1917; this was partly because a large number of mothers were away from home during the mid-day meal.

Slightly more than one-half of all the school feeding takes place in London. In 1916-17, 34,389 London children were given altogether 2,460,884 meals, at a cost to the Local Education Authorities of £57,148.

These figures should be taken into consideration with the ones previously cited showing the decrease of serious malnutrition in the London schools. It is possible that had more of such assistance been possible in this country the recent increase in malnutrition reported among the school children might have been checked. For instance, the increase in New York City schools from 5 per cent. in 1914 to 21 per cent. in 1917 might have been prevented.

That Dr. Newman fully realizes the importance of other factors than food in the health of the child is shown in his summary of the points other than medical treatment to be considered in a school clinic—a health center, if the child is to be properly educated and equipped. These issues, which he refers to as “elementary but essential,” are:

“(a) The hygiene of the child, a healthy way of life; (b) the feeding of the child, by the parent or under the Education (Provision of Meals) Acts, or otherwise; (c) the supply of fresh air for the child by means of open-air schools, playground classes, or adequately ventilated schoolrooms; (d) the exercise of the child’s body, by the adoption of an effective system of physical training; (e) the warmth and protection of the child, by requiring that it shall be sent to school properly clothed and that the schoolroom is sufficiently heated; (f) an adequate amount of rest for the child by day as well as at night; and (g) the maintenance of the cleanliness of the child, by ensuring that dirty and verminous children do not contaminate

clean children at school, and that for the school itself bath and lavatory accommodation is available."

The second section of special interest to us is the report of an inquiry into the physical condition of town and country children. This experiment was of the following nature:

"Two sets of 300 unselected elder children each, in typical London and Country Schools, to be inspected by one competent and experienced medical officer of unquestioned authority, examining all 600 children on one schedule and by one standard, a 'surprise' examination, without notice or warning, to include absent children as well as those in attendance at school, and to have regard to the effect of the physical condition of the child on its education."

The result of this examination is as follows:

Of 438 children examined, including 273 from London (145 boys and 128 girls) and 165 from the country (87 boys and 78 girls):

- 12.1 per cent. were ill-nourished.
- 26.5 per cent. had nits in the hair.
- 4.6 per cent. had verminous heads.
- 19.2 per cent. unclean bodies.
- 7.5 per cent. had verminous bodies.
- 43.1 per cent. had slightly carious teeth.
- 6.2 per cent. had extremely decayed teeth.
- 11.4 per cent. had serious defects of the nose and throat including enlarged tonsils, adenoids and mouth breathing.
- 3.4 per cent. had external eye disease.
- 10.3 per cent had serious defect of vision (less than half normal vision in both eyes).
- 4.1 per cent. had suppurative ear disease.
- 6.4 per cent. had less than half normal hearing.
- 4.6 per cent. had heart defects.
- 2.5 per cent. had lung trouble, in some cases probably tuberculosis.
- 1.8 per cent. had manifestations of rickets.
- 4.6 per cent. had enlarged thyroid.
- 2.1 per cent. had other deformities (Erb's palsy, etc.)
- 4.6 per cent. had spinal curvature.
- 6.6 per cent. had flat foot.
- 6.6 per cent. had anemia.
- 4.6 per cent. had skin disease.
- .2 per cent., one case of congenital syphilis.

Only defects of a severe degree exerting a serious effect upon the child were recorded and even then about one in five of the children examined was recorded with some defect largely remediable in nature.

The most remarkable differences were found to exist in the country and in the city in the condition of the teeth and defects of the nose and throat. While 60 per cent. of the London children had

sound teeth, only 35.1 of the country children were in the same condition. Adenoids were three to four times more frequent in the country group.

There were no striking differences in malnutrition although the country children were rosier and superior in general carriage and were freer of septic infections of the skin, the eyes, and the ears.

Many of the children examined were much behind in their studies, but the amount of defect was no greater in London in the poor class school than in the fair and good class schools due possibly to more energetic "follow-up" work.

This entire report by Dr. C. Thomas is most interesting and gives a good basis of comparison with conditions found in the schools in this country, and with Dr. Thomas D. Wood's estimate of the percentage of defects in our school children.

Unfortunately Dr. Thomas's report is not dated. It would be interesting otherwise to compare his percentage of poor nutrition in the three typical London schools given as 11.3 with that given, from 1913 to 1917, for all the London schools and specially for the intermediate grades, generally considered the worst so far as nutrition is concerned. The discrepancy between the figures for those leaving school, 6.2 per cent. in 1917, and the pre-war figure of 14.7 and Dr. Thomas's "control experiment" of 11.3 demands explanation.

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COLLECTED PAPERS OF THE MAYO CLINIC. Edited by MRS. M. H. MELLISH. Vol. IX, 1917. Pp. 831; 328 illustrations. Philadelphia and London: W. B. Saunders Company.

We have here presented the various papers published by the workers in the Mayo Clinic during 1917. Although the clinic is essentially surgical, the papers are not all surgical, the medical men and laboratory workers also presenting the results of their interesting and valuable studies. Their investigations, in the main, originate from questions arising out of the material coming to and furnished by the surgical clinic. It is this wealth of material drawn to Rochester by the fame of the Mayos which furnishes the appeal of these papers. Out of it all come many new phases of old conditions and many new demands upon the ingenuity of the surgeons who are frequently brought face to face with unlooked-for complications. Surgeons everywhere meet with similar difficulties and all are keen to know how the Mayos and their associated workers manage them. The clinical papers deal generally with subjects made interesting by some problem encountered at operation. As in preceding volumes the papers are collected according to the part of the body involved, a final group including those on general subjects. It is of interest that more space in this volume is given to papers on the

urogenital organs than to those on the alimentary tract. Nearly 250 pages are devoted to the ductless glands, heart and blood, a large part of which is only indirectly surgical. About one hundred papers are given to orthopedic surgical papers of rare interest. We find also some interesting papers on lung surgery by that authority on the subject, S. Robinson. The wide range of interesting papers from these famous writers fill up another volume which, like its predecessors, command the attention of the profession. T. T. T.

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THE EFFECT OF DIET ON ENDURANCE. By IRVING FISHER, Professor of Political Economy in Yale University. Pp. 55. New Haven, Conn.: Yale University Press.

FOLLOWING the results of Prof. Chittenden's well-known observations on the effect of diet, the conclusions of Prof. Fisher's experiment recorded in this little book are interesting. In other similar work, little attention has been paid to endurance apart from strength.

The present work has to do only with endurance. Under Prof. Fisher's supervision nine students organized themselves into an eating club. The experiment consisted of two main parts, each of which lasted about ten weeks. In the first half were noted the effects upon endurance of thorough mastication combined with implicit obedience to appetite. In the second half the same two rules were followed, and in addition the suggestion was made that when the instinct was in doubt they were to choose low proteid foods. The endurance tests were carefully guarded as to error in interpretation. The conclusions are that in an ordinary diet there is too much protein food and that the needed reduction can be almost instinctively accomplished through thorough mastication.

C. N. S.

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ABSTRACTS OF WAR SURGERY. PREPARED BY THE DIVISION OF SURGERY OF THE SURGEON-GENERAL'S OFFICE. Pp. 430. St. Louis: C. V. Mosby Company.

As an emergency war measure much of the excellent surgical work which had developed as a result of French, English and Italian effort had to be appropriated by our medical personnel. The surgeon-general's office arranged abstracts of the important general surgical papers bearing on war surgery, and after having them mimeographed distributed one hundred of them to various surgical instructors in the Army Surgical Schools and to the surgical chiefs of the war hospitals. This limited issue so far failed to meet the demand that

a wider distribution in printed form is represented by this volume. The papers abstracted are of the best quality, show careful selection, and were published in the different years of the war, a few in 1918. The best guarantee of the quality of the work is the fact that it was done in the interest of our own soldiers under government supervision. There is probably very little war surgery of value that has not been gathered in one way or another. For example, there is no abstract of Duval's great work on lung surgery, but his work is well-condensed in Moynihan's paper. The abstracts are grouped under the following headings: General topics, under which are abstracts of two good papers on the development of British surgery at the front and in the hospitals along the lines of communication; wound infection and treatment; tetanus; gas gangrene; abdomen; chest; cardiovascular surgery; joints; fractures; burns; anesthesia; trench foot; peripheral nerve injuries; and jaws and face. One could hardly obtain elsewhere a better condensation of the actual surgical experience of this war.

T. T. T.

INFORMATION FOR THE TUBERCULOUS. By F. W. WITTICH, A.M., M.D., Instructor in Medicine and Physician in Charge of Tuberculosis Dispensary in the University of Minnesota Medical School; Visiting Physician to University Hospital, Minneapolis.

THE aim of modern medicine seems to be to promote health welfare by intensive educational propaganda. This book is written with that thought evidently in mind. The author has succeeded in writing a very readable treatise that will be appreciated by patients suffering with tuberculosis. The language is untechnical, the chapters are short, and the disease, its symptoms and treatment are admirably described. It is hopeful in its tone and will undoubtedly materially aid the physician attending in his efforts to bring about a cure. The reviewer is convinced that books such as this that give to patients an accurate knowledge of their affliction are very much worth while. Dr. Joslin's recent book on *Diabetes* is along the same line.

C. N. S.

LOCAL AND REGIONAL ANESTHESIA. By CARROLL W. ALLEN, Assistant Professor of Surgery at Tulane University of Louisiana. Second edition. Pp. 662; 260 illustrations. Philadelphia and London: W. B. Saunders Company.

RUDOLPH MATAS, to whom the volume is dedicated, presents an introduction of five pages, which furnishes a very important reason

for the preparation and publication of the book. On becoming director of the surgical clinic of Tulane University, in 1895, Matas began to experiment on and study and practice methods of local anesthesia to diminish the indications for general narcosis and to substitute for the dangers of the prevailing anesthetic of the south, chloroform, the more laborious but far safer methods of peripheral analgesia. In six years they were doing 50 to 60 per cent. of the operations under local anesthesia which had previously required general narcosis. A pupil of Matas, Dr. Allen, having assiduously cultivated the technic in all its branches, presents in this volume the methods practiced and the teachings expounded in the surgical clinics of Tulane University for the last twenty years. It was the first book in our language to attempt the survey of the entire field of major surgery. The first edition, appearing in 1914, was reprinted in April, 1915, and November, 1916; but this second edition is revised and entirely reset. The key to the proper valuation of the work is that we are getting in it the results of twenty years' work at Tulane under the guidance and inspiration of Matas. The papers put out from this clinic in that time have been freely drawn from. Every phase of local anesthesia, including regional and spinal, is discussed. One is impressed by the thoroughness based upon large clinical material, with which the various methods have been tried out. The marvellous growth of local and regional anesthesia is of recent years, and few surgeons probably appreciate how far it has gone and how great are its possibilities. This volume should be in every surgeon's library.

T. T. T.

CLINICAL MEDICINE FOR NURSES. By PAUL H. RINGER, M.D.  
Pp. 286. Philadelphia: F. A. Davis Company.

THE book represents the substance of lectures on medical diseases that the author has delivered in past years to the nurses at Asheville Mission Hospital. Good judgment has been used in omitting discussion of physical signs and in concentrating on symptoms and their interpretation. It is unfortunate that on page 232 there should be a typographical error which is confusing. In a book of this kind the author cannot expect to find all his views agreed to, and the reviewer takes exception to the statement that blood-pressure estimations are of no practical use to the nurse. We feel that the technic is far from complicated and that readings have some value in diseases like pneumonia and typhoid fever, for instance.

The book, taking all in all, serves well the purpose for which it was written.

E. H. G.



# PROGRESS OF MEDICAL SCIENCE

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## THERAPEUTICS

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UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

PROFESSOR OF CLINICAL MEDICINE IN THE COLLEGE OF PHYSICIANS AND  
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**Renal Function as Measured by the Elimination of Fluid, Salt and Nitrogen and the Specific Gravity of the Urine.—II. *The Effect of High, Low and Normal Diets.***—MOSENTHAL (*Arch. Int. Med.*, December, 1918, No. 6, xxii).—In this paper (2) the author has reinvestigated the subject, using three diets (high protein, low protein and normal) on two series of individuals; the first series on normals, students and members of the teaching staff, and the second series on persons suffering from diseases causing impairment of renal function. Specimens of urine were collected at two-hourly intervals during the day and for a twelve-hour period at night. The modified standards now adopted for normals fix (1) the maximal specific gravity at 1.018 or higher for high diets and 1.002 or higher for low or normal diets. Evidently this is one of the most constant features to be relied on in estimating normal renal function by the test-meal; (2) the variation in specific gravity at 9 degrees or more, though a smaller variation does not necessarily indicate that the kidney is abnormal, provided the specific gravity is 1.002 or over, but may point to a deficient available supply of water from which to form urine; (3) in judging the night specimen only urines exceeding 750 c.c. may be looked on as exhibiting nocturnal polyuria; the concentration of nitrogen may be interpreted as normal if it is over 1 per cent., but not necessarily as an indication of diminished renal function, if it is lower. In summary, the height of the maximum specific gravity and the volume of the night urine are the most constant features of the normal test, regardless of the diet. In abnormal individuals, the comparative value of test meals for renal function on high and low diets was observed in 114 patients. Only the high and low diets were employed. It is very significant that the increase of night urine occurred almost exclusively on the high diet. In the first place, it may be concluded that nocturnal polyuria is a compensatory phenomenon to bring about the elimination of solids which a defective kidney cannot excrete except at lower concentrations than normal;

in the second place, it appears that nocturnal polyuria is a signal that the kidney function is being overtaxed and that, in some instances at least, a suitable diet may do away with this unnecessary strain. Nocturnal polyuria may be absent even when there is a marked renal insufficiency, but when present it indicates an impairment of function, especially if the night urine is increased while the patient is on a low diet. *The Maximal Specific Gravity:* This is probably one of the most important features in measuring renal function by the method under consideration. It has been previously noted how, as the activity of the kidney becomes impaired, there is a tendency for the specific gravity of the urine to assume a lower level until in the final stages it usually cannot be raised above 1.001. In comparing the results of the high and low diet, so far as the maximal specific gravities are concerned, in normal individuals, there is a fairly close agreement. Variations may occur but these are generally caused by the alternate retention or elimination of edematous fluid, and are apparently not influenced by the character of the test diet. The subject whose renal function is not impaired usually shows a fixation of specific gravity at a high level, while with an impairment of renal function this manifests itself at a much lower point. It may be concluded, therefore, that the degree of variation of specific gravity in test-meals for renal function is not very different, whether high or low diets be employed.

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**Pituitary Headaches and Their Cure.**—PARDEE (*Arch. Int. Med.*, 1919, xxiii, 174-184) reviews the various types of headaches and gives the etiology, pathology, symptoms and treatment of pituitary headache, with a report of seven cases. He concludes that (1) pituitary disturbances constitute a fairly common cause of headache; (2) pituitary headache is located between the temples, deep in behind the eyes and is accompanied by dyspituitary signs; (3) abnormality of the sella turcica is demonstrable in almost every case of pituitary disease; (4) administration of the whole gland cures these headaches and the accompanying symptoms in a large percentage of cases, provided there is not a progressive neoplastic growth.

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**Trinitrotoluene Poisoning, with Records of Five Cases.**—GREGORSON and TAYLOR (*Glasgow Med. Jour.*, August, 1918, No. 11). The author cites the clinical records of five cases coming under his observation, two of which died and were autopsied. The clinical picture is that of an acute toxic jaundice resembling the picture of acute yellow atrophy of the liver. The condition shows that there is an undoubted disturbance of the circulation of the bile ending in an accumulation and absorption of bile constituents in the blood, which leads to a severe anemia with pronounced fall in the percentage of hemoglobin, and extreme polymorphonuclear leukopenia. This new type of jaundice, as subsequent events showed, was hepatogenous in its production. A slow pulse and a tendency to mental depression, and to oozing from any wounded surface, are usually associated with the severer types of jaundice. The pulse in Case I was never under 80, was frequently 110, and, in the terminal stages, 160. Itching of the skin, which usually accompanies jaundice, was entirely absent, and oozing from the unwounded mucous membrane was a prominent feature. In Cases II and III there

was no rash on the skin, and, so far as we can gather from the history of the onset, the principal channel of absorption seems to be the lungs and stomach. A certain amount of dust must be inhaled, and a considerable amount becoming attached to the mucous membrane of the mouth and throat, is swallowed with the saliva. It has been shown that gastric disturbance and peripheral neuritis were the earliest symptoms, headache, anemia, and jaundice following in the order named. The intensity of the jaundice varied from week to week, being at times a deep yellowish green, and it was noticed that as the color faded the patients showed signs of improvement. The deepest discoloration was associated with the most serious stage of the disease. The autopsies revealed a generalized jaundice, petechial hemorrhages in the peritoneum, heart (subendo and pericardium), stomach and diaphragm. Liver: Advanced fatty degeneration. Kidneys: Advanced cloudy swelling. Brain and cord: Normal.

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**Physiological Action of Cantharis.**—MORGULIS and MUIRHEAD (*Arch. Int. Med.*, 1919, xxiii, 191-196) conclude from their investigations on dogs and rabbits that in cantharis we do not possess a means of experimentally inducing polycythemia, inasmuch as it does not cause a production of new red cells, but merely occasions a condensation of the blood through the loss of water in the process of elimination of cantharis by the kidneys.

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**Treatment of Bronchial Asthma with Vaccines.**—WALKER (*Arch. Int. Med.*, 1919, xxiii, 220-234) treated twenty-eight cases of bronchial asthma with vaccines of the bacteria to which they were sensitive; 75 per cent., were relieved of asthma and 21 per cent. were improved. Seventy-five non-sensitive patients were treated with vaccines made from culturing their sputum on plain agar; the predominating organism was usually the one selected for treatment; 46.6 per cent. were relieved and 16 per cent. were improved. Twenty-four non-sensitive patients were treated with vaccines made from culturing the sputum in dextrose bouillon and using only the streptococci; 37.5 per cent. were relieved of asthma and 25 per cent. were improved. Thirty-five non-sensitive patients were treated with vaccines made from culturing the sputum both ways: in other words, many types of vaccines were used; 31.4 per cent. were relieved and 23 per cent. were improved. Sixteen non-sensitive summer asthmatics were treated with vaccines; 31.2 per cent. were relieved and 25 per cent. were improved. Therefore, of 150 non-sensitive asthmatics who were treated with vaccines 40 per cent. were relieved and 20 per cent. were improved; these results should be compared with the treatment of sensitive patients as reported in a previous article, 75 per cent. of whom were relieved, and in this article, 75 per cent. of patients were relieved. With the sensitive cases, the age of onset of asthma, the duration of asthma and the age of the patient when treated had little to do with the prognosis; however, with the non-sensitive cases the older the patient is when asthma begins and the older he is when treatment is begun the more unfavorable the prognosis from vaccines. The permanency of relief from vaccines in non-sensitive cases depends on the individual's resistance to the bacteria in question. Some patients continue free from asthma for many months after var

cines are discontinued, others for only a month or two and some patients require the constant use of vaccines. Succeeding courses of treatment seem to relieve more promptly than the first course of treatment, providing there has been no change in the bacteria which are causing the relapse.

## GYNECOLOGY

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UNDER THE CHARGE OF

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**Mesodermal Mixed Tumors of the Uterus.**—Although this class of neoplasms is very rarely found in the body of the uterus, a number of cases have been reported, but there has been reported in this country no tumor of the uterus which contains cartilage as a heterogeneous component. Therefore the case of chondrosarcoma of the corpus uteri, originating in the endometrium, that has been reported by PERLSTEIN (*Surg., Gynec. and Obst.*, 1919, xxviii, 43) is of interest both pathologically and clinically. The clinical history is that of a woman, aged fifty-four years, whose chief complaint was profuse bleeding from the vagina at irregular intervals, which she considered as a manifestation of the menopause. Up to the age of fifty-two her menstruation, as a whole, had been regular and normal, but since then it had been irregular and profuse. She had had a curettage and roentgen-ray treatments without any permanent effect. Upon digital examination on admission to the hospital, a handful of tumor masses was removed; these masses were protruding from the dilated cervix and felt like "boiled sago." A radical pan-hysterectomy was performed and since the operation she has had practically no symptoms and has improved in every way. The pathological report of the specimen calls attention to the fact that the myometrium is soft and flabby and the uterine cavity is filled by a tumor mass which is partly polypoid and partly grapelike and attached mainly to the posterior wall of the corpus. The most conspicuous feature in the microscopic appearance is the large amount of cartilage, which in a large number of the sections is the predominating tissue, and which is found in practically every section taken from the larger polypi and berries. Perlstein states it is evident that this growth is a chondrosarcoma of the endometrium. Two kinds of tissue are predominating; namely, cartilage and a loose connective tissue. In the latter the nuclei are far apart and the tissue is myxomatous in appearance. There are also sarcomatous areas and isolated glands of the endometrial type. Besides the grapelike structure and heterogeneous components of this type of tumor, its great malignancy is one of its characteristic features, which is manifested less by metastases than by local extension and by recurrence after operative removal, which often occurs very rapidly. At first they spread on the surface; the deeper tissues are infiltrated rather late. The vaginal tumors seem to have more inclination to infil-

trative growth into the deeper tissues than those of the cervix and uterus. Distant metastases are infrequent and late and as a rule do not contain heterogeneous tissue. Clinically it is difficult to differentiate these growths from other malignant tumors of the uterus. The most common symptom is irregular and profuse bleeding; frequently there is a vaginal discharge, which at first is watery or blood tinged, later becomes purulent and offensive. A positive diagnosis can only be made microscopically and when the diagnosis has been made with certainty, the prognosis is generally considered unfavorable.

**Radium Treatment of Menorrhagia.**—The management of the profuse menstruation in those cases in which no gross lesion is found, or in cases in which a small myoma exists, has not in the past been especially satisfactory. In some instances young persons respond to glandular medication, such as ovarian and thyroid extract and pituitrin and a few patients have improved after blood transfusion, and following the use of horse serum, but the effect, as a rule, has been that of temporary relief only. Curettement is seldom effective and should be tried only after medical treatment has failed. This type of menorrhagia in older persons has usually been treated by local medication and repeated curettements. In many of the cases in which a myoma is found, the conservative surgeon hesitates to submit the patient to so radical a procedure as a hysterectomy or even a myomectomy and in such cases radium should always be considered. STACY (*Minnesota Medicine*, 1919, ii, 88) has summarized the experiences with radium under these conditions as found in the Mayo Clinic, where this element has been used in 1915 in the treatment of the menorrhagia of the menopause, in cases which presented no gross pelvic lesion, and in those presenting a fibroid but with contra-indication to operation. Since then the types of cases treated have been increased, and now radium is considered the treatment of choice in all cases of the menorrhagia of the menopause in which the presence of carcinoma is definitely excluded, either by history or by a diagnostic curettement, and in those cases not presenting a large, soft myoma which is apt to later undergo degeneration. The radium is also used in cases of profuse menstruation of the young woman (1) when there is a small submucous fibroid, (2) when no gross pathological condition is demonstrable, and (3) in cases presenting a large myoma in which there is a definite surgical risk. However, they have not entirely replaced myomectomy with radium for the treatment of myomas in the patients between the ages of thirty and forty years. Of the 175 patients that were treated with radium from August, 1915, to December, 1917, there were 2 under twenty years of age, 34 from twenty-one to thirty years, 45 from thirty-one to forty, 91 from forty-one to fifty, and 14 were more than fifty years of age. Of this number 93 had had previous curettements, 37 had had more than one curettement, and 56 had undergone other pelvic operations. In 69 cases there were complications that were considered as relative, though not in every instance absolute contra-indications to operation. There were heart lesions in 34 cases, hypertension in 8, kidney lesion in 11, obesity in 8, and pulmonary tuberculosis in 6. Seventy-seven of the 175 cases had definitely palpable fibroids and it is interesting to note that 155 of the 175 patients were married women, and that of these only 25 had not been

pregnant. The dosage of radium is gauged by the age of the patient, and by the presence or absence of a tumor. In the young person without a demonstrable tumor and when it is desirable to continue menstruation, usually one application of 50 mg. of radium element for from four to six hours is used. In older persons in whom it is desirable to stop menstruation entirely, it has been found that an exposure of 50 mg. for from ten to twelve hours has brought about the desired results. In cases in which large dosage is used, menstruation is usually irregular for about two months and ceases entirely after the second or third month; following the lighter exposures, it becomes regular and normal in most instances in about two months. It is the custom in the Mayo Clinic not to repeat the treatment until an interval of three months has elapsed. If, after that time, menorrhagia continues, a second treatment is given, and with the exception of one case, the second treatment has been effective. In this instance menstruation ceased for one year, and then became profuse and the periods prolonged. It has been necessary to give second treatments in 10 instances in this series. In 8 instances a hysterectomy was done later, but only one of these 8 patients had been given a second radium treatment. Included in this series is one case of adenomyoma of the uterus, in which a microscopic diagnosis was made at the time of the exploratory incision, but the tumor entirely disappeared after one intra-uterine and four abdominal treatments. Reports have been received from 143 of the 175 patients and in 55 (38.5 per cent.) menstruation had ceased, not to return to the date of the report. In only 14 patients did menstruation cease immediately following the treatment. In 15 menstruation ceased for three months and returned, in 29 (20 per cent.) the menstruation became normal; in 42 it was reported as regular but somewhat profuse and in 30 it became profuse. Ninety-two patients reported their condition as improved, and 27 as not improved.

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**Cost of Cancer in Norway.**—The various disasters to which death and disease give rise have an economic side, which occasionally makes itself strongly apparent. GADE (*Jour. Cancer Research*, 1919, iv, 203) has therefore tried to calculate the economic losses to Norway brought about by deaths from the cancerous diseases (carcinoma and sarcoma) in that country. These calculations are based on the one side upon the mortality statistics and on the other upon the valuation of Norwegian lives as computed by the director of the Norwegian Statistical State Bureau. As a result of this study it appears that there is an average yearly loss through death from cancer of about \$1,800,000 in this country where the population is scarcely 2,500,000 inhabitants. This amount represents only the direct loss of life-capital, and must be considerably increased if other sources of economic loss through the diseases in question are to be considered.

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**Renal Pain.**—Kidney pain is one of the commonest complaints with which the urologist is confronted and it is of great interest to the gynecologist as well. The pain may be localized in the loin or abdomen or radiate widely, and frequently neither the Roentgen ray nor urine analysis will give any clue. In order to determine the causes of renal pain, HARRIS (*Med. Jour.*, Australia, 1919, i, 41) has analyzed and studied 170 of his cases which presented this symptom and found that in

52, or 30 per cent. of the cases, the pain was caused by calculi in the kidney or ureter. In 18 cases renal tuberculosis was the cause of the pain while 32 patients had gross suppurative lesions of the kidney. This leaves 68 patients with renal pain but without any gross infection, in whom the nature of the lesion was not immediately apparent, but in the vast majority of these cases the pain was ultimately found to be due to some form of ureteral obstruction, most commonly a stricture of the ureter. Harris believes that the diagnosis can and should be made in the early stages of the disease by means of the cystoscope and the ureteral catheter, or even using pyelography if necessary, because if the diagnosis is made early in the disease, we can expect to cure the patient without sacrificing the kidney. Movable kidneys, on the other hand, should not be subjected to operation unless their causal connection with the existing pain can be unequivocally established. This is a very important statement as it has been proved many times that renal pain is seldom caused by mobility of the kidney and in many cases more harm than good is done by operative fixation of such kidneys.

**Frequency of Adenomyoma Uteri.**—Since the publication of the excellent monographs on the subject of adenomyoma of the uterus by Cullen, but few articles have been contributed to the literature. In view of the fact that his report contained only 73 (5.7 per cent.) adenomyomas in 1283 myomas of the uterus and since these figures had not been confirmed by an equally large series, it seemed opportune to MACCARTY and BLACKMAN (*Ann. Surg.*, 1919, lxi, 135) to add a report from the Mayo Clinic. Between 1906 and 1918, 3388 fibromyomatous uteri were removed in the clinic and of these 211 (6.43 per cent.) contained adenomyomas. In 5 cases the tumor was in the Fallopian tubes. The frequency is somewhat greater in this series than in that of Cullen, but the figures are so close that from 5 to 7 per cent. expresses it safely. The last 109 cases of the series were studied with reference to certain clinical features which might be intimately associated with the condition. Ninety-five patients were married: 41 per cent. gave histories of having had miscarriages, 50 per cent. suffered from profuse and prolonged uterine bleeding, and 31 per cent. from irregular bleeding. In 5.5 per cent. of the cases, epithelioma of the cervix or carcinoma of the body of the uterus was associated, neither of which conditions bore any apparent relationship to the adenomyomas. In 72 per cent. other pathologic pelvic conditions were associated, such as ovarian cysts, chronic or acute salpingitis, uterine or cervical polypi, cystic cervicitis or prolapsus uteri. In no case without the association of a malignant condition was the clinical diagnosis one of malignancy and in no case was a positive diagnosis of adenomyoma made previous to operation, but the clinical diagnosis was clothed in such terms as fibromyoma or pelvic tumor, both of which diagnoses show recognition of definite pathologic conditions of a neoplastic nature without attempting to specify in terms of detailed pathology.

**Operation for the Production of Sterility.**—It is occasionally important to sterilize a woman without removal of any of the organs and it has been found by experience that simple tying, section or even exsection is inadequate, as the lumen of the tube readily becomes reestablished

The procedure recommended by CUPLER (*Surg., Gynec. and Obst.*, 1919, xxviii, 317) has been successfully used by him during the past ten years and he has had occasion to observe the result of the operation several years after it was performed but he has never seen any attempt toward restoration of the lumen of the tube, so that he believes that it will secure sterility in 100 per cent. of the cases. In brief, the operation consists of placing a catgut ligature around a small area in the broad ligament including the bloodvessels supplying a limited part of the tube. The tube is then divided and a peritoneal cuff on the proximal end is turned back, the denuded muscle and mucosa of the tube are crushed in the bite of an angiotribe and a catgut ligature is applied in the crease, and the cuff rolled over the stump and ligated. The distal end of the tube is ligated and both ends approximated and the rent in the broad ligament closed. The opposite tube is treated in the same manner and the abdomen is closed.

**Carcinoma in a Very Young Woman.**—To those who believe that cancer of the cervix only occurs in middle-aged women, the following case which has been reported by STEIN (*Am. Jour. Obst.*, 1919, lxxix, 413) will be of interest. A young woman, aged twenty years, who had had two children and one miscarriage, complained of bleeding profusely and constantly. Four weeks previously she had been curetted by another physician and her condition was diagnosed as uterine polyp. Upon introducing a speculum into the vagina a large irregular, cauliflower-shaped mass originating in cervical tissue was found, which was extremely soft and bled upon the slightest touch. With much difficulty the uterus and adnexa were removed, but the involved iliac glands were left behind as the condition of the patient did not warrant the prolongation of the operation which would have been necessary to remove them. When the specimen was opened, it was found that the carcinomatous growth was about the size of a child's fist, originating in the anterior cervical canal and had practically destroyed the whole anterior lip. Microscopic examination showed a papillary zone of acini of polyhedral epithelial cells which are invading the surrounding tissue in all directions. In these cells mitotic figures are common, as are areas of necrosis and hemorrhage, and altogether the picture was one that unquestionably was carcinoma.

## DISEASES OF THE LARYNX AND CONTIGUOUS STRUCTURES

UNDER THE CHARGE OF  
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**A New Technic for Irrigating the Maxillary Antrum through the Inferior Meatus.**—LUC (*Rev. de Laryn., d'Otol. et de Rhin.*, May 15, 1918), having witnessed a fatal case of hemorrhage following the usual



method of entering the antrum with a sharp trocar through the inferior nasal meatus, with occasional infections of the pterygo-maxillary fossa from propulsion of the instrument after sudden penetration of the bony wall, as well as accidents from entrance of the point of the trocar into an orbital cell, determined to discard the sharp-pointed trocar for a smooth tipped rasp modelled on those used by Vacher, and by Watson-Williams for penetrating into the frontal sinuses intranasally. The rasp enables him to make an opening long enough and large enough to facilitate irrigation, and to avoid premature closure of the artificial opening.

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**Bony Occlusion of the Posterior Nares.**—WHITE, in a somewhat elaborate essay with abundant references (*Laryngoscope*, August, 1918), describes and depicts an operation of his own which he has performed with a favorable result in two cases therein reported. Under the free use of adrenalin the bony plate of obstruction is perforated with a long, flat chisel held close to the septum, and a triangular section is removed. The bone is then punched out as thoroughly as possible and the rough edges are smoothed off with a mastoid curet. The posterior end of the septum is then removed with rasp or curet and after being carefully smoothed off is covered with mucous membrane which had been previously detached and elevated for the purpose. After careful removal of all shreds and wiping the nose clean, each nasal passage is packed with a strip of gauze covered with cargile membrane or with rubber tissue. This packing should be removed in twenty-four hours, when the subsequent treatment will be only such as may be needed to keep the nose clean and free from crusts. If the operation has been done thoroughly no further packing will be necessary, nor will there be any need for wearing any device to keep the openings patent.

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**Sarcoma of Orbit Mistaken for Ethmoidal Mucocoele Successfully Removed through the Killian Incision.**—COFFIN reports (*Laryngoscope*, December, 1918) this case: After the usual Killian incision as for an ethmoidal operation, it was found that the anterior border of the naso-orbital wall had been absorbed. Dr. Coffin removed this wall well back toward the apex of the orbit cavity. The entire contents of the orbit appeared smooth and covered with an aponeurosis. As his finger moved over the surface he noted a slight depression as between two avoid bodies, and he introduced a curved periosteal elevator into this sulcus when the growth popped out free and clear. It proved to be an encysted sarcoma.

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**Epiglottectomy by Transthyrohyoid Access.**—BEAUSOLEIL in an elaborate paper (*Revue de Laryn., d'Otol. et de Rhin.*, February 15, 1919) extols an operation for excision of the epiglottis in cases of morbid growths, cicatricial adhesions from disease and injuries, and other conditions. Two cases operated upon by Prof. Moure are recorded, one for epithelioma of the epiglottis and the other for cicatricial stenosis between epiglottis and arytenoids after a wound in warfare so serious as to require immediate prophylactic tracheotomy. Neither of these cases seems very convincing as to the value of the procedure, the first

one having suffered an unconquerable recurrence, and the second one having required several surgical interventions, culminating in a necessity for a laryngotracheal autoplasty to be undertaken to cover up a large loss of tissue. The technic of the procedure is described in detail, and so is the postoperative management. In brief, it is an extensive access to the parts from a frontal incision including cricothyroid membrane, thyroid cartilage, thyrohyoid membrane and hyoid bone. It is claimed that it is the method of choice for riddance of benign tumors of the epiglottis inoperable through the natural passages, and even for malignant growths with extension into the vocal organ itself.

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**Primary Tuberculosis of Tonsils.**—OERTEL and GRIOT report (*Jour. Am. Med. Assn.*, September 20, 1918) a case of primary tuberculosis of the tonsils in a well-nourished male nurse, aged twenty-six years, in service at the base hospital at Camp Logan, Texas. The patients in his charge had been principally advanced cases of pulmonary tuberculosis. Subsequently the epiglottis and larynx became involved.

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**Acute Pulmonary Abscess after Tonsillectomies and Accessory Sinus Operations.**—TEWKSBURY (*Jour. Am. Med. Assn.*, February 2, 1918) reports a number of cases of abscess of the lung following excision of the tonsils, and operations on the accessory sinuses. Of ten cases reported, all treated by artificial pneumothorax, two died, two were only temporarily improved, and six were cured. The prognosis is poor under medical treatment. The infected organisms are carried into the lung from the field of operation by means of an infected clot with a resultant septic infarction. The symptoms appear from four to ten days after operation.

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**Angioma of the Larynx in a Child Ten Weeks Old Treated Successfully by Intubation.**—LEVBARG reports (*Laryngoscope*, December, 1918) this case. Severe dyspnea, stridor and cyanosis with marked retraction of the supraclavicular space and the upper part of the abdomen were found by direct laryngoscopy to be due to an angioma which was extending downward and which could be felt on palpation as a soft and compressible tumor. Despite the risk of laceration a six-month-sized intubation tube was introduced, and half an hour later the child became quiet and fell asleep. A strong x-ray treatment was given that day. Extubation and reintubation recurred at intervals for a week, at the end of which time the tube was no longer required and the child was so much improved that it was discharged two weeks later, the angioma still present but diminishing in size.

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**Pulmonary Collapse Consequent on Papillomata of the Larynx; Unrelieved by Tracheotomy; Death.**—MCLLRAITH reports (*Jour. Laryngol., Rhinol., and Otol.*, September, 1918) the case of a female infant twenty-two months of age admitted to hospital suffering from aphonia and stridulous dyspnea in both phases, expiration being somewhat prolonged. Papillomata almost completely blocking the larynx and projecting into the fold of the epiglottis were removed under chloroform by direct laryngoscopy, disclosing more papillomata of the right vocal cord and anteriorly and also a large, more or less sound mass attached

to the left vocal cord and apparently extending below. There was no relief from the operation and tracheotomy was performed twenty-four hours later, but this likewise failed to afford relief although expiration seemed fairly easy. Inspiration became less and less and death ensued eighteen hours after the tracheotomy. The autopsy revealed emphysema of the mediastinum and around the roots of the lungs. The lungs were completely collapsed. The collapse was attributed to the ball-valve action of the growth in the larynx which was drawn into the chink of the glottis in the act of inspiration while the expiratory acts were fairly free, and the reason that the removal of the growth and the subsequent tracheotomy had failed to afford relief was that the collapse had been going on previously to such an extent that it could not be counteracted. Further, the suction from the tracheotomy wound into the tissues and the negative pressure inside the pleural cavities would tend to increase the emphysema and promote the absorption of the residual air from the partially collapsed lungs.

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**Postericoid Spasmodic Stricture of the Esophagus.**—MCKENZIE (*Jour. Laryngol., Rhinol., and Otol.*, September, 1918) reports two cases of spasmodic stricture at the upper extremity of the esophagus. In both cases, one a woman of forty-five years of age and the other a woman of fifty, direct examination with a small caliber esophageal tube showed a definite stricture or narrowing of the lumen to a small circular orifice of from 3 to 5 mm. in diameter at the lower end of the postericoid sphincter, having much the appearance as though a thread had been tied under the mucosa. Bougies were passed without difficulty, and were kept in place for half an hour. After removal, all symptoms of stricture disappeared and there had not been any further difficulty in swallowing.

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## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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**The Occurrence of *Bacillus Influenzæ* in Throats and Saliva.**—From a study of complicated and uncomplicated cases of influenza which occurred in New York during the ebb of the epidemic PRITCHETT and STILLMAN (*Jour. Exper. Med.*, 1919, xxix, 259) report the incidence of the bacillus influenza in throats and saliva of such patients. The medium employed was Avery's oleate hemoglobin agar, on which pneumococci do not grow and streptococci very rarely, while some staphylococci show a scant growth. In influenza-pneumonia *Bacillus influenzae* was recovered in 93 per cent. of the cases. Of the convalescents studied it was found that 46 per cent. harbor the organism from one week to four months after recovery. Of 177 persons who gave no history of influenza 42 per cent. carried *Bacillus influenzae*. The authors found

that throat cultures are positive more often than the saliva, and hence are preferable as a means of isolating *Bacillus influenzae*. They also state that because of the frequent presence of other Gram-negative bacilli which morphologically may be easily confused with *Bacillus influenzae* it is useless to render a diagnosis from direct film alone. A further study was undertaken to determine the type of pneumococcus found in cases of influenza-pneumonia. Whereas in ordinary lobar pneumonia Types I and II are found with greater frequency during the epidemic, Types III and IV were most often isolated from influenza cases.

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**Endocardial Lesions Developing During Pneumococcus Infection in Horses.**—WADSWORTH (*Jour. Med. Res.*, 1919, xxxix, 279) autopsied eight horses which had been immunized against one or more types of pneumococci for varying periods of time. Interesting lesions were encountered. Some of the animals developed infectious processes locally in the joints and in the tissues of the organs, but especially in those of the heart, including the heart valves. These lesions were intimately associated with injury of the bloodvessels due to the action of the pneumococcus poisons, and were thus infectious processes in which the bacterial development was evanescent and promptly followed by complete resolution or by reparative processes with scar tissue, or the bacterial development may have persisted, inciting varying degrees of inflammatory reaction and necrosis before the bacteria were destroyed and the reparative process healed the injury. All stages of these lesions were found in the heart valves: petechial and larger hemorrhages with and without inflammatory reaction and larger and smaller areas of necrosis in which pneumococci were present in large or small numbers or absent altogether, all in various stages of development, resolution and repair. These lesions it is claimed correspond with those of acute and chronic endocarditis in man. The anatomical changes of the ulcerative or vegetative and the sclerosed lesions in man were reproduced in these lesions of the horse. The importance of predisposing injury determining the localization of the bacteria was also demonstrated, but it appeared that the bacterial poisons produced injury so that the bacterial localization was practically coincident with it or followed it immediately. It also appeared that in these experiments on the horse the endocardial lesions arose from injury of the bacteria and their poisons carried to the endocardial tissues through the coronary circulation and not from the direct action on the endocardium of bacteria and their products passing in the main blood stream of the ventricles and auricles.

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**The Fate of Typhoid Bacilli Injected Intravenously into Normal and Typhoid Immune Rabbits.**—In a previous paper Hopkins and Parker reported their findings in a study of the fate of hemolytic streptococci injected into susceptible and insusceptible animals. However, their work was unavoidably interrupted and no definite conclusion could be given. The work was resumed and PARKER and FRANKE (*Jour. Med. Res.*, 1919, xxxix, 301) state their observations upon the

fate of another organism, the typhoid bacillus when injected into normal and typhoid immune rabbits. Suspensions in saline solution of typhoid bacilli from a twenty-four-hour agar slant were injected intravenously and the animals killed at varying intervals. The organs were then carefully prepared and studied both for their bactericidal action and for the difference in localization of the bacteria in untreated and immune rabbits. The authors found that both in normal and immune animals the bacteria are taken up with extraordinary speed but they were unable to determine any constant difference in the bactericidal qualities. Technical difficulties were met with in these experiments as the animals used varied normally a great deal in their resistance to typhoid. They found that the bacteria localized more readily in the immune lung than in the normal, but they concluded that it did not seem likely that this difference can play any important part in the resistance of immune animals to typhoid as the number of bacteria taken up even in the immune lung is only a small part of the number taken up by the other organs, especially the liver.

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**Studies on Streptococci Recovered from Sick and Wounded Soldiers in France.**—This study was undertaken by MALONE and RHEA (*Jour. Path. and Bact.*, 1918, xxii, 210), using the newer methods for cultivation and classification. It was the intention of the authors to compare the infections by the streptococci in war wounds with those found in civil practice. A review of various bacteriological methods is given and the work was adapted to the most favorable methods for the recognition of different strains. The authors adopted the classification of Holman. Twenty-five cases were analyzed, the organisms isolated and classified. In the majority of instances the lesions were of the nature of wounds or abscesses in which the streptococcus was present alone or in mixed culture. Non-hemolytic streptococci were found to be an uncommon cause of surgical complications of wounds except in the cases of hemothorax where they were usually of the types found normally in the respiratory tract. The streptococcus pyogenes is the type most commonly found in infected wounds and was the most pathogenic of this group of organisms. In this respect the war wounds were similar to those found in civil practice and the danger of the patient due to infection also finds a parallelism. Out of the 25 cases, the Streptococcus pyogenes was recovered fourteen times in pure culture and three times in association with other organisms. The Streptococcus salivarius was next in frequency, occurring four times.

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**The "Reading" Bacillus on which a New Method of Treatment of Wounds has been Based.**—DONALDSON (*Jour. Path. and Bact.*, 1918, xxii, 129). The various methods of treating infected war wounds have been widely discussed in the recent literature. There have been two main schools of treatment more or less closely related, the physiological and the disinfectant. The author has started a new method which he calls the biological and which is based on the use of the "Reading" bacillus in living cultures in the wounds. The nomenclature comes from the town of Reading where the bacillus was isolated from wounds

and where it was first used in treatment. A very complete description of the morphological, cultural and biological character of the bacillus is given and these indicate that it is closely related if not identical with the *Bacillus sporogenes* (Metchnikoff), an anaërobic bacillus very frequently recovered from war wounds. The bacillus is an active spore-forming anaërobe growing in more or less woolly colonies on and in solid media and it has a very pronounced proteolytic action on a variety of protein material such as gelatin, cooked meat, Dorset's egg medium, coagulated egg white, inspissated serum and casein. The spores are very resistant notwithstanding boiling for fifty-five minutes and drying for eight months. There is no evidence that it has any pathogenicity for animals or man nor that the products of its proteolytic activity have any toxic or other ill effects. It has not been shown to be capable of attacking living tissue. One of the most important properties of this organism is its ability to destroy toxins of other bacteria, as the tetanus and the diphtheria. It has no inhibitory action on other bacteria. The rationale of the method depends on the proteoclastic enzymes which act as an organic catalyst which hydrolyzes the substrate of dead protein. It disintegrates the protein base from which pathogenic organisms operate and while so doing does not itself give rise to fresh toxic substances. This article is mainly extracted from a thesis and is a further study following a report on the same subject by DONALDSON and JOYCE (*Lancet*, London, 1917, ii, 445). The clinical results of this method of treatment of war wounds are more fully given in the earlier paper.

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**Arthritis Deformans and Spondylitis in Ancient Egypt.**—In a number of previous papers Sir ARMAND RUFFER has demonstrated a number of lesions in the tissues of Egyptian mummies indicating diseases present during the life of the individuals. In the majority of cases the lesions were localized to bones, while in a few others opportunity was still available to study changes in the mummified portions of the soft tissues. In the present study (*Jour. Path. and Bact.*, 1918, xxii, 152), completed after the death of the author by his wife and Captain Willmore, a detailed account of bone change comparable to the modern arthritis and spondylitis is reported. The studies were undertaken upon the remains of Egyptians and Nubians dating from a period of about 8000 B.C., to the early centuries of the Christian era. Opportunity was also available to the author for the study of the remains of Roman and Grecian soldiers who had invaded the Egyptian shores. Unfortunately the investigation of the tombs of the Macedonian soldiers of Alexander the Great was not completed owing to legal controversy concerning the property where they were found. In a percentage of all of these bones there were evidences of changes suggesting either the atrophic or hypertrophic types of arthritis as not a few showed intervertebral ossification, converting the spine into a rigid column. It is remarkable the frequency with which these bone lesions occurred in the bodies of certain groups. This is particularly true of the skeletons of the ancient Egyptians dating from about the third dynasty. It appears that the majority of the bodies were of individuals past middle age and that relatively few young bodies were found. It would appear that the osteoarthritis in the vertebral column was more prevalent among the ancient

Egyptians than in the more modern people. Spondylitis deformans, the author states, existed in Nubia and Upper Egypt during the pre-dynastic periods, in the early, old, middle and new dynastic kingdoms as well as during the Roman occupation and later. A careful description is given of a great number of specimens, particularly illustrating the massive osteophytes and atrophic lesions of the long bones and vertebræ. The author was even able to determine the pathological changes in which intervertebral disks were atrophied or completely absorbed in the advanced types of the disease. The study is an important one on paleopathology and is particularly interesting in a study of the antiquity of some of the diseases which are still with us. Unfortunately the study was not completed at the time of the author's death and a summary of his findings is not contained in the article.

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**Histological Observations on Normal Nerves and War-injured Nerves with the Neurokeratin Stain.**—By means of a neurokeratin stain which consists essentially of Ziehl-Neelsen carbol-fuchsin followed by 1 per cent. osmic acid, CONE (*Jour. Path. and Bact.*, 1918, xxii, 105) studied in normal and war-injured nerves especially the "renflements biconiques" of Ranvier and the vacuoles of myelin. The former he concludes are not artefacts but a part of the normal structure of the nerve, since on stretching nerves he could directly observe under the microscope the elongation and narrowing of these funnel-shaped structures. The base of the cone was attached to the sheath of Schwann and at the point of attachment, on stretching the outer border of the nerve fiber became narrowed and humped in appearance. The truncated apex of the cone was continued as a sheath for the axis-cylinder and its insertion about this structure was also rendered very distinct on stretching. With the neurokeratin stain the cones appeared mauve against the pink staining axis-cylinders. These cones were present in embryonic nerves, but only when these reached a size above  $4\mu$ . The author believes them to be bounded by neurokeratin material and that their function is connected with the growth and regeneration of the myelin in segments. This neurokeratin material he also believes to be responsible for the vacuoles or globules in the myelin sheath. These occur in young and adult nerves and the size of the globules depends upon the neurokeratin network. The "renflements biconiques" and the vacuoles, as well as nerve varicosities were extensively studied in nerves grown in guinea-pigs into which pieces of war, injured nerves were transplanted. These varicosities appeared as irregularly placed swellings in many young nerve fibers and especially in those 1 to  $3\mu$  in size. They were apparent particularly in hemorrhagic and edematous nerves and are frequently due to pressure from a neighboring nucleus or irregularities in the density of the tissues in which they occur.

## HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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**Toll of the Degenerative Diseases.—A Plan for its Reduction.**—FINK (*Am. Jour. Public Health*, February, 1919, 120-125) states that the fight against chronic degenerative diseases does not imply in the least measure a letting up against infectious diseases. On the contrary every victory in the one field is also a victory in the other, for they are closely related. The degenerative diseases are the manifestations of the accumulated effects of the infectious diseases on the individual. Nor is there reason to believe that the degenerative diseases are increasing to such an alarming extent that we are in danger of undergoing physical deterioration. There is, however, a field for preventive work against the mortality from chronic degenerative diseases, especially in the age period twenty to forty, worthy of considerably more attention than it has received. In view of the facts the author has attempted to bring out, a logical program for fighting the chronic degenerative diseases would be based upon the following: (1) Fundamentally important is the gathering and collation of such vital statistics bearing upon the subject as are available, together with a vigorous campaign for complete morbidity and mortality statistics, especially among our public institutions. It is a sad commentary on the condition of our vital statistics that the insurance companies are the only ones who possess complete records. (2) Educating the general practitioner to the possible serious consequences of mild infections. In the words of JANEWAY (*Boston Med. and Surg. Jour.*, 1916, clxxiv, 925): "The need for the moment, therefore, is for more knowledge; not more knowledge of the dangers of circulatory diseases for the public, which means propaganda, but more knowledge of their causes for the physician, which means ceaseless investigations." The public is largely dependent for its medical knowledge upon the physician; with the realization by the latter of the seriousness of repeated low-grade infections and particularly chronic focal infections, there would naturally follow an appreciation by the public of the same facts. (3) Provision for adequate medical attendance for the entire population, with appropriate sick benefits. It is well known among the medical profession that the very poor and the wealthy receive the best medical attention. The bulk of the population, the wage-earners, get the worst. Whether proper medical service be obtained by an adequate government health insurance system, or by a change in medical practice whereby people will pay for preventive medical attention, makes little difference if the



desired result follows. As a corollary to this is the extension of the periodic physical examination to include the whole population. This has turned out to be an excellent investment for those insurance and industrial corporations that have adopted it. (4) The elimination, so far as possible, of the factors of fatigue and various intoxications from the industries.

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**A Report of 7637 Schick Tests for Immunity to Diphtheria Performed over a Period of One Year.**—HUGHENS (*Bull. No. 61, Bureau of Med. and Surg.*, U. S. Navy Department, January 25, 1919) reports work covering the study of the Schick reaction in 7637 men chosen at random in the U. S. Naval Training Station, Great Lakes, Illinois, over a period of one year. He states that it would seem that an attack of diphtheria, or the administration of antitoxin as a prophylactic or curative measure, affords protection for only a short time. There seems to be good evidence that season influences susceptibility to diphtheria. It would appear that in February, March and April persons are more susceptible than at any other time during the year. The marks used were: For the minimum reaction "X," for the maximum "XXXX" and the degrees between the minimum and maximum "XX" and "XXX." The final reading of all tests was made seventy-two hours after the test was done. This reading of the degrees of reaction is, of course, an arbitrary one, and every worker must establish his own standard. It was shown that the increase in susceptibility occurred in those giving the three lesser reactions. It is evident that "X" men are on the borderline and are the ones that shift to negative in the more favorable seasons, and to "XX" increasing that class of susceptibles in the unfavorable seasons, some "XX" shifting to "XXX." Individuals shifted from negative to positive tests during the months of February, March and April, which is very suggestive that all persons become more susceptible during those months.

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**The Function of Fats in Immune Processes: II. Pneumococcus and Streptococcus Immunity.**—The work discussed in WARDEN's paper (*Jour. Infect. Dis.*, March, 1919, 285-296) is a continuation of earlier work (*Jour. Infect. Dis.*, 1918, xxii, 131), in which it was shown that the fats peculiar to certain bacteria and other cells constitute their specific antigens, as shown by complement-fixation, antibody production in animals inoculated with the antigens, and by a new specific precipitation reaction *in vitro* between the fat antigens and their appropriate serum antibodies. This paper deals with the quantity of antibody produced in rabbits from inoculations with the pneumococcus and the streptococcus fat antigens and the amount of protection afforded against the organisms. The facts brought out in the work on the functions of antigenic fats in immunity lead one to believe that such antigens are destined to play an important part not only in active immunization of animals and man as a prophylactic measure, but also in the treatment of infections. They have to commend them their purity, the dosage by weight, the absence of toxicity, the ease and safety of either subcutaneous or intravenous administration. This form of treatment would appear to be particularly applicable to the types of infections of acute and often fatal character and of brief duration where antibody production is invariably slight or

absent altogether, and where toxemia is the dominant symptom, such types being represented by pneumococcus and meningococcus infections. In infections also of a more prolonged course, such as typhoid and paratyphoid fevers, even when antibody is known to be present in the serum, as shown by agglutination tests, at the same time with the antigenic microorganism, the fat antigen would be presumed to be beneficial both by increasing the antibody production and by furnishing a nidus round which the antigen-antibody aggregate might form and lead to the absorption of complement.

**Droplet Infection and Its Prevention by the Face Mask.**—WEAVER (*Jour. Infect. Dis.*, March, 1919, 218-229) states that droplet infection comes into play whenever an individual with pathogenic organisms in the mouth gets into close contact with another individual. Sneezing and suppressed coughing are most apt to produce abundant droplet spray. Gauze will filter bacterial spray from air. Its efficiency is in direct proportion to the fineness of mesh and number of layers employed. Three layers of gauze with a mesh of forty threads or more will remove almost all bacteria-carrying droplets. Occasional fine droplets pass through. Gauze masks appear from clinical data to prevent infection through mouth droplets. They are useful when worn for protection by attendants on the sick, and also when worn by the infected individual to prevent contamination of his surroundings. The use of masks should not lead to neglect of measures calculated to prevent transfer of infectious materials by other means than droplet spray.

**Chlorinated Lime and Halazone in the Disinfection of Drinking Water.**—FANTUS (*Jour. Infect. Dis.*, March, 1919, No. 3, xxiv, 191-203) states that the desirability of possessing, in a convenient and readily portable form, a reliable disinfectant for small quantities of water, such as might be carried in a soldier's drinking bottle, has led DAKIN and DUNHAM (*British Med. Jour.*, 1916, i, 160; 1917, i, 682; also *AM. JOUR. MED. SC.*, 1917, cliv, 181) to advocate p-sulphonedichloraminobenzoic acid ( $\text{Cl}_2\text{N}.\text{O}_2\text{S}.\text{C}_6\text{H}_4.\text{COOH}$ ), under the name of halazone, as the best agent they were able to find, suitable for this purpose. The work undertaken by Fantus was chiefly to compare the value of this new agent with that of chlorinated lime. He found chlorinated lime to be a more efficient water disinfectant than halazone, compared on the basis of active chlorin. It is, of course, also a great deal cheaper. Hence there is no reason for employing halazone in water disinfection, excepting when its superior tablet-making qualities render its use advantageous. Halazone is the better agent for the preparation of water disinfecting tablets. Its action is, however, a rather slow one.

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All communications should be addressed to—

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DR. RICHARD M. PEARCE

## AN APPRECIATION OF DR. RICHARD M. PEARCE.

WITH the strain and turmoil of the war behind us, we are beginning to view the stirring and momentous events of the past two years in proper perspective. To the thoughtful it becomes increasingly apparent that victory was not alone the result of valor on the battle-fields of France. Without the widespread coöperation and thorough organization of all industries and activities in this country, the never-to-be-forgotten exploits and accomplishments of our Armies could not have been carried out. The rapid mobilization and successful direction of our vast and varied resources were made possible through the unselfishness of those leaders in all branches of work who so willingly and freely gave of their services and experience. Among this group must be numbered the many members of the medical profession who, in spite of their disappointment at being denied active service in the Army overseas, faithfully and loyally performed countless duties at home, duties which, though less dramatic and spectacular, were, nevertheless, no less arduous and exacting than those that had to be accomplished in the Army abroad. Of this coterie of patriotic physicians, none is more justly deserving of credit and distinction than Dr. Richard Mills Pearce, lately Major, Medical Corps, United States Army.

It is not our purpose here to recount his notable achievements as Chairman of the Division of Medicine and Related Sciences of the Council of National Defence, nor to dwell upon his invaluable aid to the Army when, after accepting a commission, he became closely identified with the work and organization of the Laboratory Section of the Army Medical Department. His successes along these lines are already a matter of record and are too widely known to require further comment. It is our desire, however, to give to Dr. Pearce some measure of the recognition and credit he deserves for having assumed voluntarily, in addition to his other many duties, the task of editing the AMERICAN JOURNAL OF THE MEDICAL SCIENCES while its regular Editors were absent in the military service.

Early in the summer of 1917 he undertook this work, and from then until last February he carried it on, in spite of the ever-increas-

ing burdens that were heaped upon him. The readers of this JOURNAL can amply testify to the success that attended his editorial supervision. Not only did he procure an adequate amount of material for publication, but he saw to it that the contributions published, both in scientific value and practical interest, were in keeping with the traditional standards maintained by this publication. All this he did in the face of such unprecedented difficulties as the unsettled state of the whole medical profession; the absence of many regular contributors in the Army; and the hopelessly overworked condition of those who still remained in the civilian ranks.

Therefore, it is with a sense of deepest gratitude that the returning Editors, as well as the publishers of the JOURNAL, take this opportunity of expressing to Dr. Pearce their heartiest thanks for and sincerest appreciation of what he has so graciously done, not only for them personally and for the JOURNAL, but also for the entire medical profession of America.

Credit is also due Professor A. N. Richards, Dr. O. H. P. Pepper and the others who from time to time assisted Dr. Pearce in this work.

Our thanks are likewise extended to Miss Susanna Stern, who throughout the duration of the War ably saw every issue through the press.

The Editors freely acknowledge their debt to Dr. Pearce, and fully realize that only through the personal interest and zeal displayed by him, and also by those who assisted him in his work, has it been possible for the oldest medical monthly in the United States, the one that survived the turbulent days of our own Civil War, to continue its uninterrupted existence during the world-wide struggle that has just terminated and to withstand so successfully the vicissitudes of the past two years.

G. M. PIERSOL.

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ORIGINAL ARTICLES

THE PATHOLOGICAL POSSIBILITIES OF NEGLECTED  
GALL-STONE DISEASE.<sup>1</sup>

BY JOHN B. DEAVER, M.D.,

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THE benefits of exchanging experience and discussing impressions that come to the worker in every field of endeavor are probably nowhere more apparent than in the domain of medicine and surgery; witness the numerous medical societies and associations that abound in all sections of the country, great and small, meeting at stated times to coördinate and correlate the observations that have come to their members each in his own field. It is this interpretation that I have put upon your cordial invitation to appear before you this evening, and with this idea in mind I have chosen for my subject the consequences of neglected gall-stone disease, the baneful effects of which must be apparent to every surgeon doing a large amount of work in the upper right abdomen. It is perhaps only the far-reaching effects of trifling with disease of the appendix that can compare with the consequences of allowing gall-stone disease to progress beyond certain definite limits, *i. e.*, a second attack of cholecystitis.

The varieties of gall-stone disease that most commonly lead to complications and sequels that so often are the bugbear of the surgeon, and the cause of untold suffering to the patient, to say nothing of chronic invalidism, and, in some instances, death, are chole-

<sup>1</sup> Read before the Medical Association of the Greater City of New York, April 21, 1919.

cystitis, stone in the common duct (with or without jaundice), cholangitis, pancreatic lymphangitis, chronic pancreatitis and carcinoma of the gall-bladder; for inasmuch as the three last-named are the direct result of neglected gall-stone disease, they are legitimately to be considered as varieties of that disorder.

The chief agent in the drama that often develops into such an unfortunate tragedy is cholecystic inflammation, resulting in pericholecystic adhesions, infection of the liver and the pancreas. This does not refer to the adhesions that form in ordinary pericholecystic inflammation but to the dense adhesions that are encountered in the shape of a peritoneal sheet practically enveloping the pylorus and the duodenum—in other words, pathological peritoneum, the term I use in describing the condition to my students. In addition to this enveloping membrane there are often strong bands that bind the pylorus, the duodenum, the hepatic flexure of the colon and the great omentum, and in some instances the tip of the appendix to the gall-bladder and the liver, so as to make recognition of the individual organs almost impossible. To separate this vicious conglomerate mass in certain cases would necessitate adding at least a crowbar, hatchet and trowel to the armamentarium of the operating room. This is no exaggeration; for too often it would be a serious matter even to attempt to separate such entangling alliances without running the risk of traumatic injury; gall-bladder, duodenal or gastric fistula being among the evils, and probably the mildest ones that might be expected to follow.

It goes without saying that this pathological sheet is not to be confounded with congenital peritoneal abnormalities. If I may be permitted to digress for a moment, I should like here to say that I have not met with the embryonic bands, veils and sheets of peritoneum so frequently mentioned in the literature as causative factors in intestinal stasis. I have always believed, and still believe, that they are the result of pathology, and as such only deserve serious consideration.

But these adhesions are not alone due to inflammation of the gall-bladder. In a percentage of cases they may be caused by an ulcer of the duodenum or an ulcer abutting on the pylorus that has invaded all the coats of the duodenum. This is often seen in subacute perforation of several days' standing. But whether the duodenum in the shape of ulcer is the seat of the pathology, or whether it is the infected gall-bladder, cannot always be determined until the peritoneal sheet, above referred to, is lifted. This, however, may sometimes be a dangerous proceeding, and it takes the experienced eye to judge at a glance of the wisdom of occasionally doing nothing more than performing a posterior gastro-enterostomy. It is obvious, therefore, that an effective method of preventing this aspect of the pathology of gall-bladder disease is the early surgical treatment of cholecystitis. It is an erroneous notion, all too preva-



lent even at this day, that gall-bladder disease is a surgical condition only when it has actually become gall-stone disease. Gall-stones are but one of the sequels, and, as we have seen, not one of the most important sequels of cholecystic inflammation. At the same time it should be remembered that "gall-stones are foreign bodies which need only infection to lead to the most widespread cholangitis, biliary cirrhosis and pancreatitis."

Cholecystitis is among the most frequent infections within the upper abdomen, and is also one of the most common causes of chronic indigestion. It is rarely diagnosed before middle life, because it is generally considered a disease peculiar to that period. In early life the symptoms are liable to be unobtrusive and escape recognition, but that it does occur in the twenties and thirties, and even earlier, is evidenced by the histories of our gall-stone cases and by the well-known tenacious persistence of cholecystic infection, as illustrated in typhoid cholecystitis. It is a generally accepted fact that a gall-bladder once infected rarely, if ever, resumes its normal aspect. Even after so-called cures, infection is probably always more or less active until it is removed by cholecystectomy or until it converts the gall-bladder into an atrophic functionless mass. In either case the function of the gall-bladder is dispensed with, in the second instance there is the continuous menace of degenerative reaction, while in the other the prospect is for regenerative phenomena.

To the experienced surgeon operations on the biliary passages ordinarily present few difficulties, but when confronted with the pathology I am referring to he is often staggered. Owing to the long-continued disturbance in the bladder, stone or stones at first, if wandering, may have been floated out with the bile. But later on, when they become dislodged by contraction of the gall-bladder, owing to inflammatory irritation of the bile as the result of renewed infection, they may lodge in the cystic duct, but they most commonly lodge in the common duct, occasionally in the hepatic duct, with damming up of the bile, leading to changes in the gall-bladder, liver, the intestines, etc. The gall-bladder demanding an outlet for the bile may force an opening into the duodenum. The whole area becomes masked by adhesions binding the various viscera to each other in bonds stronger than any that can be devised at the Peace Conference to hold the nations together in an amicable league. The ideal procedure, when encountering such an appalling condition, would be to remove the obstruction of the common duct and allow nature's artificial anastomosis, if I may be allowed the contradiction of terms, to remain. But the landmarks may have become so destroyed that it is impossible to locate the common duct and to provide against accidents which may happen through possible abnormalities in the regional anatomy. The gall-bladder cannot be removed *in toto* because of its close adherence to the duodenum.

How then is such a condition to be treated? The decision which will give the patient the best chance must be made quickly, with results that are not always immediately satisfactory. This is well illustrated in the following case:

Mrs. —, aged sixty-one years, for ten years had suffered with attacks of severe cramp-like epigastric pain radiating to the right shoulder, requiring morphin for relief. The attacks came on after eating, and were followed by vomiting, but never by jaundice. In the interval between attacks she was free from digestive troubles, but complained of weakness and dyspnea. Bowels were regular.

On the day of admission, March 10, 1919, to the Lankenau Hospital, Philadelphia, while shopping, she was seized with one of these attacks, which was ushered in by severe sweating. She reported having had four seizures during the past summer, the last one in August. Examination showed a well-nourished elderly woman. Slight icterus of sclera. Slight pharyngitis, with mucoid expectoration. Heart and lungs negative. Abdomen: rigidity over right side of abdomen with tenderness, most marked over the upper right rectus. Peristalsis present. No masses felt. Pulse of good tension; no sclerosis. Blood-pressure, 140; 80. Gastric analysis showed some hyperacidity.

Roentgen-rays of biliary and genito-urinary tracts were negative.

At operation the following conditions were found: The pylorus and duodenum were adherent to the liver and the gall-bladder. Pylorus separated. The gall-bladder and duodenum were so densely adherent that it was thought best not to attempt to separate them, but instead to make the inspection of the common duct safer by opening the gall-bladder and introducing the finger into it. The point of the finger, as it was carried to the fundus of the gall-bladder, entered the duodenum, showing that nature had made a cholecystoduodenostomy. The posterior wall of the gall-bladder was adherent to the common duct, which was solid with stony material. The gall-bladder was cut across and the two portions, with difficulty, dissected from the common duct—the upper portion with the cystic duct removed and the lower portion invaginated, in this way closing the anastomotic opening. The common duct thus laid bare in its first or supraduodenal portion was opened, and stones and stony debris, with foul-smelling pus removed; the latter in large amount also flowed out of the hepatic duct.

Three days after the operation the patient began discharging gastric contents through the wound and grew progressively weaker. A purse-string suture was placed (by the house surgeon) around a visible fistulous opening. This held for four days, during which time the patient improved considerably, but it broke down again and a second operation was necessary.

At the second operation the duodenum above the original anastomotic opening was partially necrosed, therefore, the only thing

left to do was amputation and inversion of the duodenum below the anastomosis, closure of the pylorus and posterior gastro-enterostomy. Immediate improvement set in, followed by complete recovery.

Stone or stones in the common duct ordinarily are not very serious if operated early. But when impaction of the duct by several stones, or stony material, takes place the state of things is serious and menacing. In such an instance the hepatic duct is also usually involved, resulting in a calculous cholangitis, occasionally with miliary abscess of the liver, that adds materially to the mortality records. The following case is an example:

Mr. —, aged fifty-five years, gave a history of indigestion for several years, with occasional attacks of severe epigastric pain, followed a number of times by jaundice. While travelling from New York to Washington he was seized with such an attack, which necessitated his interrupting his journey at Philadelphia. When I saw him several days later he was intensely jaundiced and was having two or three chills daily, followed by high temperature and profuse sweats. His liver was enlarged and tender. I advised immediate drainage of the common duct. At operation the duct was found impacted with stones the size of millet seeds, similar ones being also present in the hepatic duct. The ducts were emptied as well as possible and the common duct drained. The patient improved temporarily, but finally succumbed. Autopsy: cholangitis. Thousands of minute stones were present in the small ducts of the liver, with very many small pus foci.

May I ask what medical treatment did for these patients? Answer: Hurried the latter to an untimely grave and jeopardized the life of the former by placing her in the surgeon's hands at a time when it was nearly too late.

Diffuse calculous cholangitis holds the same relation to the liver as does multiple minute abscess formation following upon pylephlebitis, which means that all the patients die, do what you will. Moral, operate before either occurs.

Cholangitis, as evidenced by the foregoing illustrative case, is only one of the sequels of neglected cholecystic disease. The pericholecystic exudates, if allowed to progress to organization, bring with them a train of evils in the way of interference with gastric and duodenal motility, the symptoms of which are treated in various ways, but rarely in the proper way, because the correct diagnosis has not been made. What the tragic consequences may be is seen in the following instance:

Mrs. —, aged fifty-four years, for the past ten years has been suffering from indigestion, consisting of heaviness, burning sensation, eructations in the epigastrium, coming on from one-half to two hours after meals. On four occasions during this time she had attacks of severe pain in the right upper abdominal quadrant. For

the past two months vomiting spells after meals have been frequent, the last one having occurred a week ago.

Physical examination was negative, except for slight icteric scleræ and tenderness on slight pressure in the gall-bladder region. Blood-pressure, 160; 100.

At operation a mass of adhesions surrounded the gall-bladder to the right, and with the fundus of the gall-bladder, to which they were adherent, formed a hard mass the size of a tennis-ball, with the tip of the appendix adherent. After carefully separating the adherent viscera by dissecting with the knife, scissors and crowbar the gall-bladder, containing stones, was removed. The appendix, its tip containing pus, was also removed. The adherent wall of the duodenum was the site of a pressure ulcer which had gone through the serosa and into but not through the muscularis. This was oversewn.

The pathology that results from delayed intervention for common duct cholelithiasis is serious, indeed, much more serious than that produced by stones elsewhere. The effects are not local but general, from the direct influence on the physiological activities of the hepatic ducts and their radicles, through absorption by the lymphatics along the duct and from the effect on the gastro-intestinal tract by interference with the functions of the pancreas and the intestines.

Stones in the cystic duct, while not so serious, are of sufficient moment to warrant earnest consideration; for although they may cause partial or complete closure of the duct the resulting inflammation may subside and allow the duct to remain patent and permit a return to normal physiology; but the presence of the stone or stones acts as an irritant, and without doubt favors subsequent infection.

The following two cases illustrate what can occur as a result of delayed common duct and cystic duct cholelithiasis:

Mrs. —, for a number of years the subject of indigestion, which formed the premonitory symptoms of gall-stone disease, finally comes to operation (by another surgeon—a very good one, too) for stone obstruction of the common duct. The numerous adhesions caused great difficulty in locating and exposing the common duct, from which one stone was removed. He suspected that there were more stones, but on account of the condition of the patient and the difficulty he had had in extracting this one stone he introduced drainage into the common duct and closed the wound. The patient improved somewhat, but never got entirely well. Finally, at the suggestion of the original operator and her family physician, she was referred to me and we agreed that reoperation was the only course that promised permanent recovery.

The duodenum, pylorus, common duct, gall-bladder, hepatic flexure of the colon and great omentum were found to be plastered into a conglomerate mass. After much difficulty in exposing the

common duct, and with the unavoidable traumatism that would naturally occur, I succeeded in removing a rather large stone from the duct, which on being probed was then found patulous; a T-tube was introduced into the common duct. The patient recovered from the immediate effects of the operation and went along comparatively well for ten days, when she commenced to vomit at intervals of ten to twenty-four hours. The vomitus showed retention of nourishment taken several hours before. The stomach capacity and the amount of retention were determined and indicated pyloric obstruction. Posterior gastro-enterostomy was then done which was followed by prompt relief. Unfortunately, ten days later regurgitant vomiting ensued, necessitating a third operation, entero-enterostomy, for relief. This patient is now well.

The case of cystic duct cholelithiasis occurred in a young woman who for a number of years had had numerous attacks of gall-stone colic in the winter and had been in the habit of spending the summer in Carlsbad taking the cure; but the attacks always appeared again. She finally came to operation, when there was found a stone impacted in the cystic duct that had formed a union with the pylorus and had ulcerated down to the mucosa. The stone together with the gall-bladder were removed and an ulcerative opening in the pylorus oversewn; this was followed by recovery.

The patient remained well for one year, when trouble indicative of gastric retention appeared. This went on for three years, the patient relieving herself with the stomach tube, used twice daily. She eventually consulted a gentleman in your city, her home-town. Roentgen-ray examination demonstrated pyloric obstruction. It was my privilege to do a gastro-enterostomy and take out a chronically diseased appendix. The patient at the end of two years remains well and enjoys normal health.

The effects on the pancreas are as far-reaching as any of the sequels of neglected gall-stone disease, which we have been discussing, and as disastrous. The route of infection of this organ so closely allied to the gall-bladder, the duodenum and the other abdominal viscera is well known, and the regularity with which the inflammation attacks first the head of the pancreas in the form of pancreatic lymphangitis, the forerunner of chronic pancreatitis, is also a fairly well-established fact.

Pancreatic lymphangitis is nearly always related to gall-bladder inflammation, and is most easily recognized in this connection; but it also can and does result from lymphatic infection from the pylorus and duodenum, the association of duodenal ulcer and pancreatitis being not very uncommon. From personal experience I have observed peripancreatic and pancreatic inflammation traceable to an infected appendix, the route of infection being retroperitoneal and through the lymphatics along the cystic and common ducts. Unfortunately, the lesions of this prepancreatic condition

are comparatively slight and at autopsy are apt to be confused with the autodigestion of the pancreas that takes place after death. But since attention has been called to this condition, and with the present knowledge of the pathology as seen from its effects on the pancreas, which appears at the operating table, the importance of early surgery for any of the primary conditions which have been briefly referred to cannot be overemphasized.

It seems to me to be particularly unfortunate when the effects of trifling with indications of some biliary disturbances lead to the ultimate death of a young woman who has just tasted the joys of motherhood.

Mrs. —, aged thirty-two years, gave a history of three, if not six, years of gastric disturbance. Six years before her admission to the Lankenau Hospital she had complained of fulness, pain and distention in the epigastric region, followed by vomiting. The condition lasted three or four months, leaving considerable soreness in the right upper abdomen. She experienced no further trouble until three years later, when the symptoms were repeated, but with greater severity. She had since then been suffering with gaseous and acid eructations. In none of these attacks was she jaundiced. About one month before admission to the hospital, five days before the birth of her child, she was seized with sudden pain in the epigastrium, lasting a few minutes, but followed by continual vomiting until she was delivered. Three days later she became deeply jaundiced. The jaundice fluctuated once. Her stools had at times been clay-colored and the urine bile-stained. Bowels extremely constipated.

Physical examination negative except for the deep jaundice and tenderness on pressure in the right hypochondrium. After admission the patient was given castor oil, which she vomited. She then developed severe colicky pains in the right upper abdomen, radiating to the left shoulder. Relief came only after four injections of morphin.

Operation was performed ten days after admission. On opening the peritoneum a greenish-brown fluid escaped. Some fat necrosis was observed on the omentum. The gastro-colic omentum was incised, exposing a necrotic pancreas. Rather free bleeding occurred on blunt dissection of the pancreas, which was controlled by gauze packing. A distended gall-bladder was then exposed and tapped, emitting a greenish bile. Several small stones were removed from the gall-bladder.

Oozing from the wound followed during the postoperative course. Two blood transfusions were performed and calcium and horse serum administered. The wound was opened and packed with dry sterile gauze impregnated with sterile boracic acid, but death ensued on the fifteenth day after operation.

The pancreas, the most important organ of the digestive tract,

is responsible for many cases of upper abdominal distress, which we often hope to correct by removal of the appendix, and the gall-bladder. As we all are well aware, this is not always followed by entire relief of symptoms. The recurrence of symptoms after gall-bladder operations is a favorite topic of discussion among surgeons. On the strength of my experience in these conditions I am of the opinion that it is necessary to go further, and when the condition of the gall-bladder permits in not a few instances, I make it a practice to do cholecystoduodenostomy. The removal of the gall-bladder, the site of interstitial changes, in the presence of enlargement of the glands along the cystic and common ducts, will in some cases fall short of bringing about the desired result. In those cases where, in addition to enlargement of the above-mentioned glands, the glands beyond and more intimately related to the pancreas are enlarged, it is my practice to do an anastomotic operation; this seems to correct the condition and to bring about a restoration to the normal. I have done this again and again, with most gratifying results.

That carcinoma of the gall-bladder may result as a sequel to calculous cholecystitis cannot be denied. Recently, I operated for a condition diagnosed carcinoma of the hepatic flexure of the colon. The patient, a woman, aged seventy years, had been a constant sufferer from upper abdominal discomfort, which had been at various times interpreted as gall-stone disease. When I saw her in consultation the most pronounced symptoms were pain, nausea, marked constipation, exhaustion and weakness after a bowel movement, secured only by purgatives, loss of weight, anemia, later confirmed by the blood picture. Examination revealed the presence of a hard tumor in the upper right abdomen, which was confirmed by the roentgen rays. This, together with the symptoms, suggested carcinoma of the colon. At operation I found a diseased gall-bladder filled with stones, and upon its inner wall, midway between the fundus and the neck, a carcinoma adherent to and infiltrating the great omentum, which in turn was adherent to the serosa of the hepatic flexure of the colon, indenting the bowel so as partly to obstruct its lumen.

I have refrained from touching upon the more remote possibilities of cholecystic infection, such as subdiaphragmatic abscess and sub-hepatic infection, which often are difficult to deal with. A discussion along these lines would hardly be germane to my subject, except to call attention to their importance in relation to what has gone before.

I shall be satisfied if what I have said proves of value to the surgeon and convinces the physician of the dangers of persistent medical treatment for conditions which, as I hope to have succeeded in demonstrating, surgery alone can relieve. I do not hesitate to maintain that medical treatment is to a great extent responsible for many of the dire results I have portrayed. Somebody is certainly at fault. Who is at fault?

**SPECULATIONS REGARDING THE NATURE OF CANCER.**

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**RELATION TO ACIDITY.** The writer has previously called attention to the fact that about three-fourths of all cancers arise in parts that either have an acid secretion or are prone to acid fermentation. With more or less variation in actual proportions, this can be verified from any statistics. It is partly coincidental, to the extent that a large proportion of epithelium is exposed to acid contact while mesoplastic tissues are never so exposed physiologically and only exceptionally pathologically, but, comparing the epithelium of the alimentary canal, including its offshoots into the liver and pancreas and its less direct embryological extensions, according to reaction, a very great preponderance of cancer is noted in parts subject to acid contact. It is not intended to claim that the actual fact as to preponderance of cancer in acid parts is significant nor has it been possible to test the significance by a therapeutic application of a hypothesis as to the influence of reaction on the growth of cancer.

**ESSENTIAL IDENTITY OR DIFFERENCE OF CARCINOMA AND SARCOMA.** Both these diseases and the less common types of malignant new formation, including even leukocythemia, present analogies to infections, and while every germ thus far claimed has been disproved, the same was true of syphilis until quite recently, and yellow fever, scarlet fever and other diseases of undiscovered germs are almost unanimously regarded as infectious on account of general characteristics. The alternate theory that the cancer cell is its own germ, while supported by considerable authority, is, when analyzed, not materially different from the claim that a man can lift himself by his own boot-straps. Whether the malignant diseases are held to be infectious or not there is no general established principle which enables us either to affirm or to deny that malignant involvement of different types of cells is due to the same essential cause and hence constitutes one disease. Conversely, it is equally impossible either to affirm or to deny that there is one essential disease, carcinoma, including epithelioma and cancer of various types of epithelial cells. Thirty years ago much was written regarding the distribution of disease according to embryonic layers. The easy generalizations at first suggested were shown to be inaccurate and the whole subject deserves careful review in the light of modern methods and accumulated knowledge. If cancer, involving epiblast and hypoblast, is essentially one disease, there may also be a unity with sarcoma affecting mesoblast, and, on the other hand, neither



unity nor severalty necessarily depends on this argument. Valuable hints could be obtained even from statistics regarding the joint or sequential occurrence of different types of carcinoma or of carcinoma and sarcoma or of other essentially malignant processes. Reports of such a nature are surprisingly few. The writer has seen pyloric cancer occurring ten years after an extirpated breast cancer and has encountered a very few analogous reports. Just enough cases of this kind are on record to prevent a negative conclusion and not enough to warrant a positive one. However, the extreme rarity of such concurrences or sequences should not influence our general conclusion. Most of the so-called malignant diseases, aside from carcinoma, are extremely rare, even sarcoma being by no means common. The marked and fairly prompt fatality of the malignant diseases in general reduces the possibility of an occurrence of two types in the same individual to an almost infinitesimal proportion. For example, considering the ages at which sarcoma, on the one hand, is common in the sense of an incidence well within 1 per cent. and at which carcinoma is common in the sense of 10 to 20 per cent. of those dying at a given age, the chances of a survivor of the former being attacked by the latter disease is very small, much smaller than might appear from a direct application of the law of chance, for we must consider also the intermediate deaths from intercurrent causes. Even the application of the law of chance to the far commoner types of carcinoma as at present designated in a broad sense is, superficially, only about 5 per cent. of the 10 per cent. that recover at the most, and scarcely 1 to 1000 with due allowance for intercurrent deaths. Supplement this small proportion with the difficulties in the way of obtaining accurate clinical histories and securing their availability in statistical form, and it will readily be seen that the problem is extremely difficult. Yet the actual observation of malignant cases is at times sufficient to warrant the expectation that the problem is soluble, at least in a negative sense. For example, Kolb<sup>1</sup> reports on cancer observed in Bavaria, 1905-07, as follows: Males, 877 malignant tumors, including 288 sarcomas (3.28 per cent.); females, 11,266 malignant tumors, including 300 sarcomas (2.66 per cent.). The care with which the statistics were gathered is indicated by the fact that the location is unspecified in only 196 males and 286 females. He makes no note of carcinoma and sarcoma occurring in the same individual. In passing, it may be remarked that the volume of mesoblastic tissues is enormously greater than that of either hypoblastic or epiblastic or both. This has no special bearing on the question of the identity or non-identity of the two diseases as the resistance of various tissues to well demonstrated infections, such as diphtheria, pneumococcus disease, etc., is equally marked.

<sup>1</sup> Ztschr. f. Krebsforsch., 1910, vol. viii.

**THEORY OF RESTS.** Inspection of the statistics mentioned shows almost at a glance that the vast majority of cancers occur in organs in which epithelium in the strict sense, hypoblastic or epiblastic, is frankly available. The exceptions are as follows:

	Males.	Females.
Spleen . . . . .	3	4
Peritoneum . . . . .	164	531
Pleura . . . . .	32	33
Kidneys . . . . .	67	45
Lymph glands . . . . .	17	7
	283	620

Of course, the occurrence of cancer in an organ containing epithelium does not directly discredit the theory of rests, and it is plausible to believe that they would be more common in tissues of the same kind, yet the theory would receive much stronger support from the frequent occurrence of cancer in organs in which either epiblastic or hypoblastic cells are not normally present. But it is not merely the general rarity of cancer in non-epithelial organs which militates against the theory of rests. The peritoneum, pleura and kidney which account for the large majority of this list of cancers are questionable in a double way. It is not absolutely established whether endothelial cells (a most ignorantly coined word etymologically) and those from the genito-urinary cell mass are mesoblastic or not, and hence, whether the cells can or cannot be properly included as epithelial and their malignant degeneration as cancer. Aside from this point, the great preponderance of peritoneal cancers in women strongly suggests that they were not primary but arose from the genital epithelium well known to account for the general preponderance of cancer in women, while the possibility of error in designating a lymph node as the primary seat of cancer needs only to be mentioned, especially considering the fact that secondary involvement is almost invariable. With these qualifications the numbers presented are too small to support any contention. It must not be forgotten, however, that even if it were shown that all true cancers occurred primarily in organs containing epithelium, as the vast majority certainly do, this would not absolutely disprove the theory of rests.

**EPITHELIOMA.** Without absolute statements as to identifications, the following cases may be considered as in all probability epithelioma, involving epiblastic cells:

	Males.	Females.
Skin of face . . . . .	4	5
Other skin . . . . .	13	24
Head . . . . .	146	185
Neck . . . . .	42	29
Trunk . . . . .	21	34
Extremities . . . . .	25	29
	251	306

2.95 per cent. males and 2.67 per cent. females of all cancers, excluding sarcoma.

It is scarcely likely that the designation or failure to designate "skin" as a localization has any significance, except in a few cases, aside from the group of cases included under "head" where involvement of muco-cutaneous and mucous membrane and of certain interior structures is probably a considerable factor. The paucity of cases in the groups plainly implying skin involvement in the great majority of instances may perhaps be taken to indicate two important facts, though the probability of greater resistance of dermal epithelium and certain other qualifications must be taken into account. These facts are the relative lack of importance of traumatism in either the chemic, thermic or mechanic sense, in the etiology of cancer and the absence of an infectious agent susceptible of development by direct implantation. While the skin of the body generally may be regarded as protected by clothing from both of these etiological factors, that of the face, hands and neck cannot be. In particular, if traumatism and exposure were appreciable factors, we should expect a notable incidence of cancer of the face in men, from shaving, and a notable excess of cancers of the neck in women from relatively greater exposure. Incidentally, allusion may be made to a statement that I have seen somewhere, to the effect that 1 per cent. of all deaths, not merely from cancer, were due to skin cancer, in spite of the facilities offered for early diagnosis and extirpation. This statement is surprising if true.

**RELATIVE SUSCEPTIBILITY OF EPITHELIAL TISSUES.** It would be interesting to know the relative susceptibility of each organ proportionate to its vulnerable tissue. In the absence of anything approaching accurate figures the following approximate estimates may be given. The area of the skin and of the mucous membrane of the alimentary canal is about the same—15,000 sq. cm.—but in males the former has 2.956 per cent. of all cancers, the latter 74.6 per cent. In females the respective ratios are 2.674 per cent. and 50.2 per cent., or, excluding genital and mammary cancers, to make a fairer comparison and revising the percentage basis accordingly, the ratios are 3.7 and 69.4 per cent. In other words the susceptibility of the internal (not entirely hypoblastic) epithelium is twenty to twenty-five times as great as that of the skin. How far the two areas compare in number of cells or mileage of tubules is not known.

For the solid organs a similar but not closely analogous comparison may be made thus:

	Liver.	Pancreas.	Both kidneys.	Thyroid.
Weight, ounces . . . . .	48 to 58 males 40 to 50 females	3	9	1
Percentage of all cancers, males	6.3	0.6	0.9	0.3
Same, females	7.2	0.5	0.5	0.5
Same, females, adjusted to male figures by excluding genital and mammary cancers . . . }	9.9	0.7	0.7	0.5

It appears, at first sight, that there is some approximate relation between the size of the organ and the incidence of cancer, but closer consideration fails to show anything like a close approximation for the smaller glands while the apparent proportionate incidence for the liver is probably due to the well-explained development of cancer subsequent to that of the pylorus or adjoining parts and to the inability to distinguish in statistics between secondary involvement of the liver and true primary growths.

A comparison of the liver and the brain, organs of approximately the same weight and far larger than any other viscera, shows about a tenfold higher incidence in the former, but subject to the same qualification as to the distinction of primary and secondary growths. In the brain about 0.9 per cent. of male cancers and about 0.6 per cent. of female cancers occur. But the physiological conditions are obviously very different, the epithelium of the brain is epiblastic, that of the liver hypoblastic, and the epithelium of the brain highly specialized and not so voluminous in proportion to the total bulk of the organ. Moreover, brain tumors include a disproportionate number of sarcomata and variously classified neoplasms, for which allowance in collated statistics of large series cannot well be made.

The following estimates have been made of the incidence of cancer in various parts of the alimentary canal:

	Area in sq. cm.	Males.	Females.	Females exclusive of genital and mammary cancers, per cent.
Esophagus . . . . .	50	4.2	1.1	1.5
Stomach . . . . .	1960	55.2	38.3	52.9
		0.5	0.2	0.3 stomach and esophagus.
		3.3	2.8	3.9 stomach and liver.
		59.0	41.3	57.1 stomach including extensions.
Duodenum . . . . .	340	5.7	4.9	6.8 intestine except rectum.
Rest of small intestine . . . . .	8800			
Large intestine to rectum . . . . .				
Rectum . . . . .	300	5.7	2.9	4.1

Other approximate estimates have been made that, roughly speaking, gastric cancers outnumber intestinal cancers 10 to 1 and that cancers in or near the rectum outnumber those of the rest of the intestine in about the same ratio. The writer's personal experience scarcely coincides with the above indication of the much greater frequency of esophageal cancers in the male. In approximate correspondence with area of epithelial surface it will be noted that the esophagus is at least as liable to cancer as the stomach even if we ascribe borderline cancers to the latter and consider female statistics, while, if we consider male statistics and give the benefit of the doubt to the esophagus, the proportionate incidence is nearly three times as great for the latter. A similar comparison shows that the rectum may be said to be from a little more susceptible than the

stomach up to twice as susceptible. On the same basis of comparison the stomach, with approximately one-sixth the epithelial area of the intestine, has eight to ten times as many cancers, or, in other words, shows somewhere from fifty to seventy times as much susceptibility. No larger statistical series that the writer has seen distinguish accurately enough between cancers of different parts of the intestine to enable even an approximately accurate arithmetic comparison to be made, but, considering the general acceptance of the rarity of cancers between the duodenum and the rectum, or, at least the lowermost part of the sigmoid, it is not far from the truth to say that the parts of the alimentary canal subject to alkaline digestion show a susceptibility of about one-hundredth that of the parts subject to acid digestion and acid fermentation. But this is not the only factor to be considered. The esophagus, for example, is highly liable to thermic, chemic and mechanic insults, but, on the other hand, is protected by a copious and tenacious mucus, not to mention the differences in cellular histology. With rare exceptions of unusual nature the intestine is entirely free from thermic traumatism, only rarely subject to mechanic insults or even to chemic irritation beyond those inevitable to its own physiology.

RELATION OF SEX TO CANCER. It has been commonly held that while a somewhat higher incidence of cancer occurred in females, this was mainly on account of the special vulnerability of the sexual organs, including the breasts, and that there was a reduced proportionate incidence of cancer of other organs in the female, perhaps not quite balancing the strictly sexual cancers, but nearly so. It is possible to juggle statistics in various ways, and, even without intentional bias, to arrive at somewhat different interpretations, according as we do or do not take account of the slightly different proportionate numbers of males and females in a given population, according as we estimate death-rates according to general population or that of age groups or compare deaths from a given cause, for example, cancer, with all deaths in the same age group or other unit. Again, as pointed out especially in an article in the *Med. Record*, April 18, 1914, males and females die at different rates in different age groups, there being for most areas an initial higher birth of males and a correspondingly higher number of male deaths until sexual differences, primary and due to habits of life, afford strictly sexual reasons for death. In this country especially, and perhaps almost exclusively, on account of immigration, males predominate in the population, though an exception exists in the case of several Eastern States from which males have migrated in considerable numbers to the West, so that there is a preponderance of male deaths until the age group seventy-five to seventy-nine. Thereafter there being an excess of old women over old men and the duration of life being obviously short, deaths of females are in excess.

Again, for a considerable period of middle and rather advanced life, the mortality rates for men in any given age group compare more closely with the next or the second junior age group for women, while, at extreme ages, there is a tendency toward equalization. Thus, for anyone who really tries to make a fair comparison, the problem is quite complicated. But however one attacks the problem, it appears that the commonly accepted idea of the influence of cancer of the sexual organs on the total cancer incidence of the sex is erroneous. For example, if we subtract the sex organ (including mammary) cancers from the total cancers of women, as indicated by the actual number of deaths, we find fewer female than male cancers, for any recent census year in the United States. But the difference is almost exactly the same as that between male and female deaths in general and is nearly proportionate to the excess of males in the population, which, in turn, is due mainly to the excess of immigration of males. In other words, if we eliminate for the moment all consideration of cancer of the female sexual organs (including the breasts) the cancer deaths and undoubtedly the incidence is almost exactly the same, proportionately for the two sexes. The proportionate occurrence of cancer in various organs aside from the sexual is not quite the same for the two sexes, but, in general, there is not a great difference, and especially not for the organs of maximum incidence, although there are some details more or less explainable, as the notably smaller incidence of buccal cancer in females (better care of mouth and teeth, less irritation from smoking). Cancer of the sexual organs of the female may therefore be regarded as an element added to an approximately equal incidence for other organs.

**LOCUS MINORIS RESISTENTIÆ.** If we regard this principle as meaning that an individual is, for various reasons, to be infected or affected with a given disease somewhere and that the localization alone is to be determined by local conditions, permanent or temporary, the above fact may be interpreted as an argument against the conception that cancer is a general disease. That is to say, if merely the location of a cancer depended on local conditions the excessive liability to cancer of the sexual organs in females would, as is generally believed, lessen its incidence in other organs, which is in general not true. It is scarcely necessary to state, however, that this conception of *locus minoris resistentiæ* does not apply to any disease. Thus there is sound reason for regarding cancer not as a condition to which an individual is doomed by law of chance or by extrinsic causes and that the cancer, being obliged to locate somewhere is, so to speak, attracted to one or another organ but as a disease, whether infectious or not, whose development depends upon susceptibility of the part in which it actually does develop. In this sense it must be granted that cancer is at the beginning a local process. But like various other diseases necessarily having a

lesional location, it is also general. One need not repeat the argument as to the general nature of diphtheria, pneumonia, etc. The conception of cancer as a local process must also be qualified in a narrow but very practical sense. Even dermal lesions which offer the best opportunities for early diagnosis and relatively accessible but more or less concealed cancers cannot, under present conditions, be successfully eradicated in more than a quarter of cases even when their destruction is resorted to promptly.

**CAUSE.** As stated there is at present no direct evidence of a germ and no indirect evidence, geographic, racial, dietetic, etc., pointing to any definite extrinsic cause of cancer. Except by analogy from neoplasms of the lower animals which are not necessarily identical with human cancer, even though histologically similar, there is no valid evidence of a specific infectious element, such as exists without reasonable doubt for various diseases, including several exanthemata of undiscovered germ. The word germ, by the way, is used without apology, to indicate the broad nature of the etiological problem in this regard. The development of cancer seems to depend upon the susceptibility of a special part of the body but no plausible predisposing cause, as age, *per se*, or as indicative of metabolic changes, traumatisms, gross or mild and repeated, preëxisting non-cancerous lesions, general state of depression or bad hygiene has, so far, been satisfactorily reduced to the "with or without" test. That is to say, no plausible cause assigned as favoring the development of cancer in a given case, necessarily has the same result in all or even the majority of cases while, on the other hand, cancer of any part may develop without any of the plausible causes used to explain other cases. In plain words, we cannot prophesy with more than a small chance of fulfilment that any exposure or lack of caution, or antecedent disease, will result in cancer. The proportion of fulfilments is indeed so small that we can scarcely regard it as more than a coincidence. About the only advice we can give to prevent the development of cancer, and even then without absolute assurance, is not to subject any part to a repeated irritation of any kind, not to bear children, and to die before the age of forty.

**IMMUNITY AND SUSCEPTIBILITY.** It has been well established that heredity plays no notable part in cancer. Given a large family in near generations, or, what really amounts to the same thing, a familiarity with family history, almost any cancer case will afford a history of cancer in the family. Otherwise, instances of apparent family tendencies are shown to be pure coincidences by the sporadic occurrence of other cases without similar family history. There is no evidence that anything approaching specific immunity explains the incidence or non-incidence of cancer. So far as can be judged, its occurrence is either according to the law of chance or due to local susceptibility. As previously implied, if it could be shown

that a cured case was immune, very definite conclusions could be drawn. But, on the one hand, the chance of a subsequent independent involvement with cancer of a case from which cancer has been removed and which has survived for a sufficient length of time to warrant a belief in cure, is very slight, so that the infrequency of such cases is no argument for the acquirement of a true immunity; on the other hand, that such cases occasionally occur shows that such an immunity is not absolute.

## HEART MUSCLE EQUATIONS.

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To the average general practitioner—in fact, to many of us who considered ourselves internists—the recognition of myocardial disease depends almost entirely upon evidence either of marked arteriosclerosis or upon the presence of irregularities in the heart-beat. The teaching in the schools does not go beyond this point. That a man might be free from symptoms, have sufficiently good cardiac compensation for the needs of his daily life, might have a normal blood-pressure, no signs of an arteriosclerosis and no irregularity of the pulse, and yet might have a serious defect of his myocardium, is generally not recognized. The mass of data accumulated during the war has given a new insight into this question. Dealing, as we did at Camp Greenleaf with men who were in general above draft age, a great opportunity was presented for the study of lesions of the myocardium.

While the methods of examination are those in use in a cantonment, as applied to men under military control, slight modifications in the type of exercise prescribed between examinations of the patient and the use of tact in employing the functional tests should make the methods of equal value in civil practice.

In order to have a clear idea of the factors concerned in determining the "work value" of the heart, mention of some of the well-known points in cardiac pathology and physiology may be worth while. Any infectious process, whether it be tonsillitis, pneumonia or "grippe"—which is usually a streptococcus process—scarlet fever, typhoid fever, diphtheria, as well as the better recognized etiological factors—rheumatic fever or syphilis—can and usually does cause some damage to the heart in greater or lesser degree. These infectious processes, of whatever sort, leave behind, as a rule, a point of least resistance in the heart; hence, not only is the chance of further



damage to the heart greater with each succeeding infection, but since the action of the disease is, to a certain extent, selective in its attack upon the cardiac tissues, a recurrent infection of a particular variety is more to be feared than is infection with a variety of different diseases. For instance, repeated attacks of rheumatic fever will generally show a greater effect upon the heart than would have been the case had the individual had but one attack of rheumatic fever, and, at other times, pneumonia and scarlet fever. Of particular importance from the point of view of eligibility for army service is the fact that some of the chronic disease processes in the heart tissue are, regardless of further infection, cumulative in their action; in other words, the end-result of a series of bacterial invasions of the heart progresses of itself in severity with the passage of time, from a process which at first was of little importance to a disabling condition. Finally, and by far the most important fact of all in the practical application of cardiac pathology, a fact frequently ignored on the part of physicians, there is, usually, an involvement of the heart muscle in most infections of the organ. We have been accustomed to consider the damage that these diseases do to the heart merely in terms of the endocardium—in particular to the valve segments—when, as a matter of fact, the valve defects produced were in many cases of less far-reaching consequence than the damage to the myocardium that went hand in hand with the endocarditis. Above all else in the estimation of the capacity of the heart muscle to do work, this fact—namely, that infectious diseases do, as a rule, produce damage to heart muscle and that this resulting damage to the myocardium is, as a rule, not discovered until much later than the accompanying valve defect must be borne in mind, for it is absolutely fundamental to the conception of the problem.

We know that if the heart muscle be fully competent its reserve power is so great that even a very serious valve defect, such as a mitral or an aortic regurgitation of marked grade, can be overcome by the intact muscle without any backing up in the lesser or in the greater circulations respectively. In the same way a normal heart muscle will compensate by hypertrophy for the work necessary to overcome the resistance of a narrowed valve opening. Up to an indeterminate point the heart valves may be very seriously damaged without any break in compensation if the power of the pump is undiminished. Hence, for the quantitative and qualitative estimation of the power of a particular heart we must consider as factors in the reverse order of their importance (1) the valvular defect if any; (2) the maximum work required of the heart, and (3) the competency of the heart muscle.

Taking the criteria as to the condition of the myocardium in the order in which we reach them during the routine examination, we may lay stress, to a greater or less degree, upon the following: (1) Blood-pressure determinations; (2) the quality, rate and volume

of the radial pulse; (3) the force of the apex impulse; (4) the length, loudness and quality of the first sound at the apex; (5) the presence and character of the second sound at the apex; (6) the character of the sounds over the lower part of the right ventricle and the comparison of the sounds at this point with the sounds at the apex; (7) the effect of exercise upon the quality of the first and second sounds at the apex and over the right ventricle, with a comparison of the sounds at these two points; (8) the "effort test," as such, with relation to pulse-rate, dyspnea, cyanosis, cough and distress; (9) the presence and quality of the sounds at the base; (10) the presence or absence of relative signs of cardiac decompensation, such as edema at the bases of the lungs, edema of the extremities and the causation, as a result, of exercise of a systolic murmur at the apex, not to be heard before exercise; (11) the presence or the increase as a result of exercise of irregularities in the heart-beat; (12) various formulæ for the determination of cardiac power by means of exercise, blood-pressure readings, pulse-rates or by combinations of these factors.

While in some instances a more thorough conception as to the condition of the heart muscle might be obtained through the use of the electrocardiograph or the polygraph, these instruments are often not available, and they are by no means indispensable to a very accurate determination of the function of the heart of a given person.

Two simple facts upon which I wish to lay particular stress are these: (1) our problem deals with a complex human mechanism and not with a machine; hence, it can never be reduced to the terms of machinery, and errors are bound to occur at times; (2) if sufficient time is taken and a sufficient number of observations are made in cases of doubt, very few errors will be made. In a large percentage of cases thoroughly accurate and satisfactory work cannot be completed under a week or ten days.

The routine, when the necessity for speed in the completion of the physical examination has not shortened the examination to a period insufficient for the best work, is as follows: The systolic and diastolic blood-pressures are taken with a mercury instrument, the subject being in a sitting position. The pulse-rate is then counted with the man standing, the quality of the pulse wave and the condition of the radial artery determined, and if there is present any tachycardia, or in cases in which it is desired to make the standard "effort test" of the Army, as prescribed for draft boards, the pulse-rate is again taken with the subject recumbent. The location of the apex-beat, percussion of the borders of cardiac dulness and auscultation over the apex, over the tip of the right ventricle, along the line from the apex to the aortic area and over the pulmonic area, is made in the usual way. Suspicious sounds are listened to with the subject recumbent, and he is then tested as to the work coefficient of his heart muscle in either one of two ways. The "effort

test," as laid down for the draft examinations, requires that a man shall hop 100 times in succession upon one foot. This test is thoroughly effective, and although the work done by one subject will differ from that done by another to a degree greater than is the case when using the "staircase test," because one man will hop higher or will bend his knees more than another, yet this disadvantage is outweighed by the economy of room, of time and of apparatus. When used to determine the presence or absence of the "effort syndrome" the pulse-rate is taken in the recumbent position, and the subject then takes the 100 hops, the pulse-rate recumbent being taken again immediately. Normally, after 100 hops the pulse recumbent should return inside of two minutes to within five beats per minute of the preëxercise rate. If the pulse returns within these limits of time and rate the effort test is said to be normal for that individual and the so-called "effort syndrome" is thereby excluded. In dealing with older men, with men who are, as a rule, flabby of muscle and who are being examined more with regard to the competency of the myocardium than for the presence of an "effort syndrome," a somewhat different procedure is followed. While perhaps in many cases the completion of the standard test might give us some information, yet, in so far as the heart muscle is concerned, there is much less to be learned from the heart-rate, particularly in dealing with nervous individuals of middle age, than from other phenomena; and since few men of middle age, physically untrained, are able to complete the 100 hops without exhaustion and the risk of actual damage to the heart, these same men will show up any deficiency in the power of their heart muscle with a much smaller amount of exercise *in most cases*. Usually, I request the candidate to hop upon either foot until I ask him to stop; and he is made to hop 20 to 40 times, depending on his age and weight or until he seems to be tiring. When the man completes his full 100 hops he has done an amount of work that is almost certain to bring to light any defect in his heart, whereas, in a few cases, the compensation in a particular individual may lie, let us say, in the neighborhood of 60 hops; if he be made to hop 80 times he is certain to exhibit proof of decompensation, which will be overlooked at the end of only 40 hops, because for this individual 40 hops are below the limit of the reserve power of his myocardium. Hence, this is a source of possible error. Another possibility with the effort test as concerns the chance of error, lies (1) in the fact that graduated exercise may increase compensation to a point above the ordinary demands upon the cardiac reserve—in which case we may consider such a heart to have reëstablished its title to our full confidence; and (2) in the fact that rest may build up the reserve of a seriously weakened myocardium to a point where it is able to stand a limited amount of work, and apparently to prove itself above suspicion through an apparently good effort test, although the seeming change

in the muscle is in reality of only brief duration. This last type of error can be almost automatically avoided by a sufficient period of probation and by making the function test—the ability to withstand the strain of repeated graduated exercises—of a less severe type than the hopping test.

To return to the routine examination: One has the candidate exercise by hopping and then one listens to the sounds at the apex, over the right ventricle and at the base, as before, comparing the first and second sounds with each other at each point; also comparing the quality of either sound at one point with its quality at another point. One considers not only the quality of the sound but also whether any murmurs, inaudible before exercise, are now to be heard. Sometimes the patient is then reauscultated recumbent. Under these procedures cases fall into one of three classes: Those coming within normal limits; those who will not be injured by a moderate amount of graduated routine exercise, such as setting-up exercises and company drills; and those definitely unfit for active exercise at the moment. In the determination of these categories the age, the weight, the habits as to exercise and the possibility of a recent attack of an infectious disease must be taken into consideration. Those cases fit for drill and not in the "normal" class are allowed to do all of their company duties short of violent exertion for a week, returning at the end of that time for a reëxamination exactly like the first; and if the disposition of the case cannot then be determined, they return again two days later. Those cases not fit for drill are reëxamined at two-day intervals until the condition present is self-evident. In all abnormal cases it has seemed to me that at least one reëxamination was essential, as any heart case, whether the defect be of the myocardium or of the valves, will change in physical signs from day to day; and since most of our candidates were nervous regarding the examination, had just completed a long journey and were usually suffering from constipation as the result of the change in living conditions, a much fairer picture as to the true condition existing in the heart could usually be obtained on the second examination.

Taking up the points of greater or lesser value in the estimation of heart power, let us start with the determination of systolic and diastolic blood-pressure. Later on I shall discuss some of the various formulæ used with the blood-pressure readings as factors; but to begin with, I shall take the single determination, in the sitting position before exercise, of the systolic and diastolic readings. Incidentally, after personal use of the spring instrument for many years, I have had an opportunity to rediscover the mercurial manometer, with a great deal of satisfaction. As I pointed out in a previous paper on the physical examination of recruits<sup>1</sup> with men of the educated classes, and especially with those who are at all nervous, the systolic blood-pressure is usually elevated. How much of this

is due to a recent long journey, to the change in environment, to the habitual constipation from which, in my opinion, practically all physicians and others of sedentary habit suffer, or to pure nervousness, I do not know. Since there is a limit to the amount of very strong tea or coffee and tannin decoction which a man can imbibe, and since the drinking of water falls off very greatly in cold weather, since also the urines in these examinations showed an almost invariable increase in specific gravity—averaging 1.026 to 1.040—to such an extent that my impression of the average specific gravity found at Camp Greenleaf, was that it lay in the vicinity of 1.030—I feel that constipation, habitual or recent, plus a decreased fluid intake, is responsible for the elevated systolic pressures, at least in many cases. What we must, I think, admit is that we actually know very little as to the significance for good or ill of either the systolic or the diastolic pressure. While I believe that a systolic pressure of over 150 or under 115 indicates some condition—probably either a toxemia or a change in internal secretion—unfavorably affecting vasomotor control, and that the redetermination of the pressure and a search for the cause thereof should be made, I do not feel that there is any definite proof as to the power of the heart muscle contained in the single determination of systolic and diastolic pressures. Many observers hold that a diastolic pressure of over 100 indicates a myocardial defect. I cannot see the facts in that light. Who has any proof as to this or any other theory regarding blood-pressure? My contention is, if we admit, as many observers do, that a systolic pressure of 160 may be perfectly normal for a man, aged fifty years, and that the diastolic pressure should maintain its relationship with the systolic, approximately in the ratio as two is to three, then with a systolic pressure of 160 we ought to expect a diastolic pressure of 105 to 110 as a normal counterpart to the systolic pressure.

In a particular individual the apparent size of the radial artery, the volume of the pulse wave and the tension of the pulse depend to a very great extent upon the conformation of the arm and the degree of adiposity of the individual. Hence, while the force of the pulse is a good indication as regards a recent infection, and may help us in the diagnosis of an acute myocarditis, it is of much less value than is the blood-pressure reading as regards the heart power. The volume of the pulse, other than in so far as it shows individual variation, is of help only in the diagnosis of a valve lesion, or in estimating the change in conditions in one subject from day to day. The pulse-rate may be either a help or a hindrance in visualizing heart force. A rapid pulse-rate may indicate nervousness, irritable heart action, an active absorption of toxins from a lung focus—either tuberculous or otherwise—from the tooth sockets, nasal sinuses or the intestine, or perhaps a thyroid hypersecretion; or, on the other hand, it may be the only sign left of a pancarditis

originally involving the heart valves as well as the myocardium. Cases have been frequent here, where there was a persistent tachycardia, associated with a very slight involvement of the mitral valve, either with signs of a very slight stenosis or regurgitation, with a good response of the heart to work tests, and no other indication of fundamentally serious damage to the heart except the frequency of the pulse. Judging from my observation of children who at one time had definite disease of the mitral valve, and who some years later showed no signs whatsoever of the valvular condition, but who did have this same tachycardia, I am inclined to believe that, as the only sign of a damage to the myocardium of slight extent, a rapid pulse-rate is much more common than it is supposed to be. The use of the pulse-rate in the estimation of the work efficiency of the heart I have already discussed.

The force of the apex-beat is no safe guide as to the capacity of the heart for work. A thick chest wall will often cushion the apex push of a competent heart; a dynamic heart action or an hypertrophied although seriously damaged myocardium will give us, on the other hand, a very forcible impulse. Here, the existence of emphysema of the lungs may play a part in the result.

The length, the loudness and the quality of tone of the first sound at the apex is of great importance. In the case of a normal heart muscle the first heart sound at the apex has a forceful, muscular tone, and is of a good length. If the first sound at the apex becomes "booming" in character it usually indicates increase in the work demanded of the heart, and one usually finds present either an hypertrophy of the heart, an increased blood-pressure or an increased aortic second sound. It is my profound conviction that all of the signs just mentioned—hypertrophy, hypertension and increased aortic second sound—combined with a moderate cyanosis, can be produced, and are very often so produced, as the result of a chronic intestinal stasis, even when the individual is having a daily bowel movement. They, of course, occur frequently in thyrotoxicosis. As was mentioned in the case of the apex-beat there are several conditions other than weakness of the sound, which may make the first sound at the apex seem weak. This may be due to the mere physical distance of the apex from the stethoscope, either from the thickness of the chest wall or the presence between the heart and the ear of emphysematous lung. Sometimes it may happen that the heart merely swings away from contact with the chest wall, in which case, by getting the subject to bend forward so as to place the heart in the closest possible contact with the chest, one will at least have the best possible conditions for auscultation. Quite often the heart sounds are almost inaudible except at the base of the heart. As a rule, this is the case only in large elderly men with a slow pulse, or at least a pulse that is not rapid. When the heart sounds are so very distant our examination is almost com-

pletely limited to the effect of exercise on the pulse-rate and upon the heart sounds. If the response to exercise in these two respects conforms to the criteria which will be described later, then we may safely assume, according to my experience, that the individual has the necessary heart power even if the heart sounds when he is at rest seem disconcertingly vague and distant.

In my opinion neither a mere "roughening" of the first sound, ending with the end of the first sound, nor a reduplication of the first sound, which is to be differentiated from a presystolic murmur by the absence of the crescendo pitch and the abrupt ending of the latter, detracts from the muscle quality of the sound, and they are to be noted merely to differentiate them from murmurs.

Do most of us give much thought to the second heart sound heard at the apex except in so far as it may be double or may be accentuated, both of which conditions merely suggest a possible mitral stenosis? It was not until I had been experimenting on the work value of the heart for some months that I became interested in the weakness or absence of the second sound at the apex of the heart. What is the cause of the presence or the absence of this sound, which, of course, is propagated to the apex from the base of the heart? Opinions seem to differ on this point, some observers believing that the position of the heart and the conditions of the lungs as regards emphysema are responsible for the absence of this sound at the apex. My own view is that, barring marked emphysema, the second sound can usually be heard at the apex if the subject be made to bend forward, and that a failure to hear this sound indicates a defect in transmission from the point of origin, presumably with an accompanying muscle defect. Whether the second sound heard at the apex is the aortic or the pulmonic sound, or both, or whether it may vary in different individuals or in the same individual at different times, depending upon the preponderance of the aortic or of the pulmonic second sound, I have not determined to my satisfaction. Of only one thing in this connection do I feel certain: If the first sound at the apex, and with the subject leaning forward, has not become appreciably more distant as the result of exercise, as sometimes happens in marked emphysema, then the second sound at the apex should be audible after exercise. Failure in the quality of the second sound after exercise, even with the subject bent forward, indicates to me a defect in the myocardium.

Another valuable standard as to the interpretation of the sounds at the apex, and one which is peculiarly adaptable for reference in each particular case, since each man carries his own standard with him, lies in the comparison of the sounds over the tip of the right ventricle with those heard over the apex. This observation was first pointed out to me by Le Roy B. Crummer, of Omaha. The best point at which to listen is usually about an inch and a half to the right of the apex, roughly, in the fifth space at the left sternal

margin. Normally, the sounds over the right ventricle at this point are much less loud and are more distant than those at the apex, but normally the first and second sounds are heard well at this point. While as the result of disease the sounds here may share equally with those at the apex in the loss of muscular quality of the first sound and the clearness of the second sound, yet the damage to the left ventricle may be much greater than to the right or the change in the sounds may be due to emphysema. In any case, without marked emphysema, if the sounds over the right ventricle, and in particular if the first sound at this point is louder than the first sound at the apex, it indicates, I believe, a loss in the muscle tone of the left ventricle.

Stress has been laid on the importance of the quality of the first heart sound at the apex with the subject at rest. Much more important information is to be obtained from a study of the first sound after the subject's heart muscle has been put through its paces by means of the effort test. *Exercise should increase the clearness with which the heart sounds are to be heard*, except in the presence of a marked large-lunged emphysema. The first sound at the apex should improve in loudness, in length and in sharpness as the result of work. The second sound at the apex, if audible at this point before the effort test, should be increased by this procedure, in my opinion, if the muscle be of good capacity and there be no marked emphysema. If, as a result of exercise, either the first or the second sounds at the apex lose in quality, in loudness, in distinctness, I believe that, in the absence of an emphysema, we have proof of a defect in heart-muscle function. Whether the enfeeblement of the second sound at the apex after exercise be due to a change in the relative accentuation of one or the other second sounds at the base, to a change in the force of closure of both pulmonic and aortic valves, or to a change in the conductivity of sound on the part of the heart muscle, does not, to my mind, alter the significance of a weakened second sound. Also of very great value, I believe, is the comparison of the relative strength, or loudness, of the sounds at the apex and the sounds over the right ventricle as affected by exertion. As stated above, the sounds, both first and second, are normally louder over the apex than over the right ventricle when the man is at rest. This relationship, to my mind, should also hold good after the work of the heart muscle has been increased. If the sounds over the right ventricle, as the result of the effort test, become more accentuated than those at the apex I feel that this would indicate either an enfeebled power of the left heart or a backing up in the lesser circulation increasing the work of the right heart, whichever way one wishes to state the case. While it is, of course, conceivable that a marked emphysema should make the heart sounds more distant after exercise, yet with a condition marked enough to do this the interposition of emphysematous lung between the heart and the



chest wall should work equally over the apex and the right ventricle; hence, I do not consider that emphysema should cause an increase in the sounds over the right heart at the expense of the sounds at the apex. Here, again, in comparing the sounds at these two points, one should remove all possible source of error by having the subject bend forward.

Perhaps the most important evidence of all in estimating the cardiac function is provided by the production of symptoms as the result of the effort test: (1) Dyspnea is to be considered. Here a certain amount of caution is to be observed. Increase in heart work, with its increase in pulse-rate, will, of course, produce a certain degree of increase in the rate of respiration; if this stops short of markedly rapid breathing we cannot speak of dyspnea. With real dyspnea there should be more or less actual air hunger, as evidenced by a deeper breathing, use of the accessory muscles of respiration or movement of the *alæ nasi*. In other words if the circulation is really embarrassed we should have some signs of distress. There may be present a flushing of the face, and some increase in cyanosis may occur as further evidence. Provided that there is not some self-evident process present in the lungs, the causation by exertion of an irritative cough is also presumptive proof of lack of power on the part of the left heart. One symptom, not ordinarily thought of and not referred to in the literature as a sign of fibrous change, in the myocardium, is the production, with or without other signs of decompensation, of a high degree of exhaustion, with an accompanying lassitude of surprising severity, out of all proportion to the amount of exertion needed to produce this symptom. While in the military service such statements must be taken with reserve, in private practice I feel that the complaint of undue exhaustion from such every-day occupations, as carrying moderately heavy weights, running for a street car or putting a tire on a car, should be viewed as of considerable importance, both in the diagnosis and in the treatment of a weakened heart muscle. While, as stated before, the full "effort test" is not, as a rule, gone through with, one can judge accurately enough in most cases as to the effect of work upon the heart rate by observing the degree of acceleration of the pulse after 20 to 40 hops and the promptness with which the heart action again becomes quiet. One caution with regard to the estimation of the degree of dyspnea is necessary. Psychic causes, such as excitement, a belief that there is something serious the matter with the heart, a neurotic temperament or a desire to avoid military duty, may all cause a veritable moving picture of dyspnea, with gasping respiration, marked distress and every appearance of utter fatigue, regardless of the severity of the exertion. I suppose that the most stupid of individuals is able to double the rate of his breathing, and often the less real the condition and the more self-pity the individual possesses the more realistic picture of abject exhaustion is he able to present.

With regard to the second sounds at the base not very much information of value regarding the heart muscle is obtainable. While an increase in one or the other of the second sounds at the base is of very great value in suggesting further study of the vessels, of the kidneys or of the lungs, except in so far as an increase of marked degree in the sharpness of the pulmonic second sound at the base suggests a deficient emptying of the left ventricle, no definite weight regarding the myocardium can be placed upon increase in the second sounds at this point. A decrease or an absence of second sound over the aortic or the pulmonic area suggests more a possible defect or anomaly of the valve in question than any change in the muscle function.

It would seem to be self-evident that in the absence of a valvular lesion any evidence of cardiac decompensation is necessarily proof of a defect of the cardiac muscle. Probably no one will disagree with the opinion that the presence of edema at the bases of the lungs or of edema of the ankles is proof of such decompensation. Even here a certain amount of caution is to be observed, as in a given case such decompensation may be purely related to flabbiness and fatty deposit in the heart or to a lack of the habit of strenuous exertion; and these signs may soon disappear after the man has become accustomed to the amount of work which he is required to do. So far as I can see, such must be the case with all heart muscle when taking on greater loads of work than that to which it is accustomed, and it is the purpose of all athletic training to increase the work power of the heart in just this way. Hence, again, a reason why it seems to me impossible to render a just and accurate decision as to the power of a given heart in one examination. Another source of error in respect to swelling of the ankles lies in the fact that the present uniform lends itself to undue confinement of the legs, and that many men, either from ignorance or from vanity, lace their breeches or strap their leggings to a degree interfering with the circulation in the lower leg. This I believe to be the case to a greater degree when a man first enters the service than later on in his military career. The most important sign, in my belief, of a decompensation of the heart lies in the production, as the result of exercise, of a systolic murmur at the apex, there being no murmur audible previous to the effort test. About the significance of this fact there seems to be some difference of opinion; in other words, there is a difference of opinion as to the physiological means of production of this murmur. In practice I think that any murmur which is of cardiorespiratory nature, and which disappears when the subject stops breathing, should be excluded from the type of sound that I am discussing. Personally, I am convinced that where there is no murmur heard at the apex of the heart when the subject is at rest the appearance of a constant murmur, systolic in time, usually short, and following the first sound without pause, the murmur persisting

for a longer or shorter interval as the heart quiets down, is to be accepted as evidence of an acute dilatation of the heart, and that the resulting murmur is due to a relative mitral regurgitation produced by the stretching of the mitral valve ring. Whenever this "breaking" of the first sound into a murmur as the result of the effort test occurs I feel that a diagnosis of a myocardial insufficiency can be made without question. Whether this myocardial weakness is to be taken as evidence of an actual myocardial disease or not depends again upon the previous habits of the individual as to exercise; and naturally enough, more exercise will be required to produce this sign in one defective heart than in another.

Furthermore, the man, although having a relative mitral insufficiency, may have enough muscle compensation to take care of the extra heart work required by this regurgitant stream of blood and may show no sign whatsoever of distress; in exactly the same way that a heart with an actual rather than a relative regurgitation might readily be able to carry the extra load without symptoms, yet in neither the case of the relative nor the actual regurgitation do I feel that we can accept the absence of symptoms as a proof of the freedom of the heart from defect. To my mind the presence of a relative mitral regurgitation without valve lesion, as evidenced by the appearance of a systolic murmur after exercise, is proof of a very definite lesion of the heart muscle.

Irregularities in the heart-beat may or may not be of significance as to muscle function. Ordinarily the occurrence of infrequent extrasystoles, which is the commonest form of irregularity, is of no importance; and, as a rule, under the influence of exercise, the irregularity disappears. When the extrasystoles become more frequent after exertion, or, what is more common, when the irregularity becomes more frequent a few minutes after the effort test than was the case before added work was put upon the heart, this would seem to indicate a considerable degree of change in the heart parenchyma. The presence, whether at rest or after work, of a gallop rhythm, persisting during several examinations, is believed to indicate a grave injury to the myocardium. Among men, especially in those who have been accepted for military service, auricular fibrillation is an extremely rare condition. In the examination in the military service of more than 30,000 hearts, for which I have been responsible, I have seen only two cases of this condition, one of them without concomitant valve lesion; the other of the paroxysmal type, disappearing entirely while under observation. Of course, when present, this condition is of serious import as regards the soundness of the heart muscle. The other irregularities of the heart need not be mentioned in detail, as they are either self-evidently of evil omen, are rarely found, or carry with them other conditions in themselves also serious. One exception that I may make to this last statement relates to simple pauses in the hear-

beat, that is, apparently dropped beats, both at the wrist and over the precordium, in which the polygraph tracing showed a complete pause both in the auricle and in the ventricle. In this condition, of which several very marked cases have been observed in soldiers, there was apparently present a simple sinus arrhythmia of no prognostic or diagnostic importance. While it is not in the ordinary sense an arrhythmia, an alternating pulse, one strong and one weak beat alternating, properly should be spoken of here. It is believed to indicate damage to the myocardium.

In the discussion of the various formulæ for the determination of cardiac function the following are worthy of consideration.

**THE STAIRCASE TEST OF SELIG.** The pulse is counted and the systolic blood-pressure taken. The candidate then ascends twenty steps rapidly, the pulse-rate and systolic pressure being taken again at once. Normally the pulse-rate rises twenty beats; the systolic pressure rises 8 to 10 mm. Selig considered that the time of the return of the blood-pressure to normal was an index of the degree of myocardial defect. This test, or modifications thereof, is much used, but the standard set as to blood-pressure by itself is not of definite value.<sup>2</sup>

**GRAUPNER'S BLOOD-PRESSURE CURVE.** After taking the systolic pressure and the pulse-rate the subject is given a definite amount of exercise, and when the pulse-rate has returned to the preëxercise rate the systolic pressure is again taken. If the systolic pressure after exercise remains constant, Graupner considered the myocardium to be normal. If the blood-pressure falls as the result of exercise the muscle is insufficient; if the blood-pressure rises and then returns to normal there is present compensation of the heart; while if the pressure rises, then rapidly falls and does not rise again the heart muscle is in a state of fatigue.<sup>3</sup> Cabot and Bruce, experimenting with this test, believe that it gives valuable information.<sup>4</sup> Personally, I believe that, while a persistent fall of blood-pressure following exertion indicates in general a possible myocardial insufficiency, there are so many factors outside of the heart muscle entering into the problem that the test is not wholly dependable.

**THE CARDIAC EFFICIENCY FACTOR OF TIEGERSTEDT.** This employs the equation:

$$\frac{\text{Pulse-pressure} \times \text{pulse-rate}}{\text{Systolic pressure} \times \text{pulse-rate}} = \frac{\text{velocity}}{\text{work}} = \text{coefficient of the pumping power of the heart.}$$

The pulse-rate may be omitted from the above equation, leaving merely the relation between pulse-pressure and systolic pressure, normally a ratio of 1 to 3. Tiegerstedt holds that any increase in this ratio whereby the pulse-pressure approaches the systolic pressure represents heart weakness.

**THE CARDIAC OVERLOAD FACTOR.** This is practically the inversion of the above. Normally, pulse-pressure is to diastolic pressure

as one is to two. Stone holds the view that the approach of the pulse-pressure nearer to the diastolic pressure represents overload on the heart.<sup>5</sup>

Whether one makes one's equation using the pulse-pressure with the diastolic or with the systolic pressure as the second factor, respectively, does not actually make much difference, since the equations are very likely to be reciprocal, and in many cases no value can be placed on either the Tiegerstedt or the Stone formula. As stated before it would seem that the diastolic pressure should follow the systolic pressure upward, in the normal ratio, except in cases in which aortic insufficiency, hyperthyroidism or "effort syndrome" is present, and that a disturbance of this ratio indicates an abnormal condition, though not necessarily of the heart muscle.

GOODMAN AND HOWELL'S FOUR PHASES OF BLOOD-PRESSURE. The estimation of the length of the four phases of the blood-pressure as determined with a stethoscope over the cubital space, seems to me to be too empiric and too difficult of accurate determination to be a practicable means of judging heart power.<sup>6</sup>

Equations having as factors the pulse-rate and the systolic and pulse-pressures, standing and recumbent, with or without the effect of exercise upon these factors, have in my experience no advantage over the simpler tests and formulæ. After all, all of these formulæ are merely attempts, very praiseworthy and very desirable as such, to solve a problem that does not seem possible of solution by any mathematical equation. If we knew what we were dealing with in studying the question of blood-pressure, if we really knew what any of the factors of which we speak so glibly really meant, if we really knew what caused the changes in any of these factors, then we might be able to make a chart that would show what was to be deduced from a given combination of factors. For example, we do not know what the systolic pressure represents except perhaps the peripheral resistance as maintained by vasomotor control. We say readily that diastolic pressure is the mean pressure, that it is determined by the end of the third phase through the stethoscope, that it represents the power of the heart muscle, but we do not know any of these things as facts.

CONCLUSIONS. I. No single procedure or formula gives universally applicable information regarding the integrity of the heart muscle in a given case.

II. In the order of their value as indications of a damaged myocardium, I would place the following criteria:

1. The general appearance of the subject, with special reference to his color, to the occurrence of actual dyspnea, or distress, or cough or exhaustion resulting from exercise.

2. The presence of a true gallop rhythm at rest or following exercise.

3. The production, as the result of exercise, of a relative mitral insufficiency, as evidenced by a murmur.

4. The presence, in the absence of valvular disease, of signs of decompensation, as edema of the lungs or of the extremities, whether at rest or after exercise.

5. Weakening of the first sound at the apex, resulting from the effort test.

6. Increased strength of the first sound over the right ventricle as compared with the first sound at the apex, occurring after exertion.

7. Weakened first sound at the apex, at rest, in the absence of emphysema.

8. The production, following the effort test, of irregular heart action or the increase in irregularity, already present, brought on by exertion.

9. Loss or weakening of the second sound at the apex, due to exercise.

III. Variations in the systolic, in the diastolic or in the pulse pressures are believed to give relatively little information regarding the cardiac function.

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### ADVANCEMENT IN THE TREATMENT OF WOUNDS AND INFECTIONS RESULTING FROM THE WAR.

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WHAT effect will the experiences of surgeons during the war have on the civil practice of surgery? Has the treatment of wounds been revolutionized? Has any new antiseptic been discovered since the beginning of the war which will prevent or arrest infection? Will experience in the treatment of war wounds change our treatment of wounds in civil practice? What have the men who have been working in military hospitals really learned?

These are the questions which one has constantly put to him by members of the profession and by intelligent and inquiring laymen, and, although the answers cannot always be categorical or perhaps satisfying, yet it has seemed worth while, now that the war has terminated, to take stock of our experiences and to try to estimate of what real value they have been. In doing this I shall endeavor to bear

diseas. mind that only a small proportion of my readers are surgeons and  
xtremis. et that all are interested in a general way in this subject. The  
eld is a large one, any portion of which is worthy of high-powered  
results study, but it will be looked upon on this occasion as a whole, and  
with but a very low lens.

he right First, it may be said without question that, as a result of this war,  
negative the treatment of wounds and infections has been advanced enor-  
on the mously and that this advancement must undoubtedly influence the  
practice of civil surgery.

intere Again, it may be said that the man who found himself in a posi-  
nt, les tion to carry out the treatment of wounds in the advanced hospitals,  
or even in the base hospitals alone, had at least an opportunity to  
apex learn a great deal and should benefit greatly from his military  
experience.

in the The men who served their country without being fortunate enough  
ion me to do so in the field of their particular medical or surgical training  
and experience, the men who filled executive positions or acted as  
regimental surgeons, made much more of a sacrifice and deserve  
much more credit than those of us engaged in that line of medicine  
or surgery in which we were interested before the war and which  
we expect to follow now that the war is over. It is true then that  
he who made the greatest sacrifice is the one who will gain the least,  
from a professional point of view, by his experience.

As to the question of new antiseptics, there is not nor will there  
ever be an antiseptic that can supplant the aseptic treatment of  
wounds; that is, there is nothing we can use which alone will prevent  
a contaminated dirty wound, probably containing foreign bodies,  
from becoming an infected and suppurating wound. The war has  
definitely taught one great lesson in the prevention of wound infec-  
tion, it is immediate and complete mechanical cleansing, what the  
French call débridement, what we might call mechanical antisepsis.  
It is difficult to find a single term to express just what this means;  
the word "excision" has been employed a great deal and Crile has  
made use of the term "revision," but neither, and certainly not  
the latter, is a comprehensive term. This mechanical cleansing  
is the most important step in wound treatment and the care with  
which it is carried out determines the proportion of wounds which  
may be immediately and completely closed and the proportion of  
infections and deaths from infections. Time and technic are the  
factors in the beginning. To close a wound immediately and  
completely it must be prepared for this closure with care and  
thoroughness; there must be the certain removal of all foreign  
materials and of all injured and contaminated tissue. Immediate  
débridement and complete primary suture without the use of  
chemical antiseptics constitutes the ideal treatment of a gunshot  
wound, and it is remarkable what results may be accomplished with  
care and experience. Before this war no one would have dared in

operating upon a gunshot wound to have closed the wound without a drain, and if he had done so there can be little doubt that a serious infection would have followed: and yet this is exactly what was being done in hundreds of cases every day during the last year or two of the war, not because of the employment of any germicidal agent, but through the practice of painstaking removal of everything in the wound which might infect it.

But there must of necessity be a large majority of wounds which cannot be immediately closed; the lapse of sufficient time for infection to occur between the receipt of the wound and the operation, say ten to fifteen hours, varying with the situation and character of the wound, the presence of comminuted bone and the necessity for immediate transportation, all render immediate suture unsafe. In order to render the ideal treatment possible, these wounds must be treated before contamination has produced an infection and the surgeon must be able to keep the patient under his immediate observation for at least two weeks. It is apparent then that it is during the so-called "quiet periods" that the best work can be accomplished; but even during the times of the greatest activity, with sufficient surgical teams, thorough débridement or mechanical cleansing can be accomplished and the closure of the wound may be done later when the patient has reached a hospital where he can remain until healing is complete.

One of the difficult things to give up was partial closure of wounds with the introduction of some form of drainage. Partial closure is an error, however, because it is much easier to sterilize and close a wound secondarily which has been left wide open than one which is partially closed with a drain. Hundreds of wounds were closed by what is called "retarded primary suture" within three or four days at a base hospital after an early débridement done nearer the front. Before this war, sterilization and closure of a large suppurating wound was rarely thought of and still more rarely practised, and yet this was the object of all treatment at the close of the war; and, moreover, it was accomplished in the large majority of cases.

Primarily the credit of successful wound sterilization is due to Carrel and Dakin, but certainly the surgeons in the American service owe much to Depage, Le Maistre, Duval and others who have elaborated or simplified the technic.

Here, again, just as in the primary operation, the success of the treatment depends upon the care with which it is carried out. Half-hearted effort only results in indifferent success. It was remarkable to see the different results obtained by different men and in different hospitals where exactly the same types of wounds were treated and supposedly the same method of treatment employed.

The most important factor in this sterilization is the thoroughness with which the primary operation is done, for if the surgeon should leave any foreign material, such as a piece of metal or a por-



tion of clothing, or even a portion of devitalized tissue, sterilization becomes difficult or impossible; and the second most important factor is the proper employment of the sterilizing agents. In the American hospitals where the best results were obtained the Carrel-Dakin treatment was employed. If this treatment was properly used, practically any wound free from foreign material was sterilized and closed.

The Carrel-Dakin treatment in infected wounds is one of the big things surgery has gained by the war, and the man who says there is nothing in it, that it is too cumbersome or that there are a number of other methods just as good, has either never seen a hospital where the treatment was being properly used or else he is so hide-bound that his opinion is worthless. I am afraid a number of American surgeons had this idea upon their arrival in France, but I am thankful to say that most of them became early converts to the method, and those who did not certainly were never able to produce results comparable to those obtained by the men who perfected themselves in the employment of the method. I never appreciated what this treatment was capable of accomplishing until I saw it properly employed in Carrel's own hospital at Compiègne, and then I was ashamed of my own wards. His wards contained scores of cases with large open wounds in the process of sterilization, and rarely was there a drop of pus to be seen. By adhering closely to the Carrel and Depage technic I am thankful to say we were able later in a number of our hospitals to duplicate their results.

I am not prepared to say that other agents, such as dichloramin-T, will not sterilize infected wounds, but I do think that there is no method so universally applicable and reliable as the Carrel-Dakin treatment, and this statement is not made on personal experience alone, but also on a fairly wide observation in many American, French and British hospitals.

There are two criteria for judging the germicidal power of any of these agents—the fall in the bacterial count, as shown in smears and cultures, and the ability to close the wound completely. No method that cannot stand these tests is worthy of consideration. In my opinion the bacteriologist is an absolutely essential factor in retarded primary and secondary closure of wounds, and I say this in spite of the fact that many surgeons became very expert in determining by clinical evidence only what wounds might be safely closed.

In no field of war surgery has the advance been so remarkable as in the treatment of gunshot wounds of joints. These wounds in our own Civil War were always treated by amputation or followed by severe infection, which frequently caused death or necessitated amputation. Up to the beginning of this war any surgeon who operated upon a gunshot wound of the knee-joint, for instance, and closed it without drainage would have rendered himself liable to a malpractice suit; and yet at the end of the war a surgeon who

did not close such a wound was open to the criticism of not doing up-to-date surgery. The results warrant the change in practice, for drainage invariably meant infection of a more or less serious nature and infection meant more or less incapacitating ankylosis or even worse. I have seen a straight series of ten gunshot wounds of the knee-joint, with fracture in all but one, treated by four surgeons (Pool, McWilliams, Jopson and Heuer) at Evacuation Hospital No. 1, heal by primary union and the patients leave the hospital with movable joints. And still can anyone doubt that surgery has advanced since and as a result of the war?

That these results can and must be obtained in civil practice is equally patent. Since my return to civil practice I have operated upon a pistol-shot wound of the knee-joint in which one ball perforated the head of the fibula, caused a gutter fracture of the condyle and a comminuted fracture of the patella, and another ball entered through the shaft of the fibula and perforated the head of the tibia. Early débridement was done in this case and the wounds closed without drainage. Primary healing took place and the man left the hospital within a few weeks with considerable motion in his knee-joint. I am sure that without my own military experience behind me, or that of others, this man would today still have discharging sinuses and probably a stiff knee-joint.

Another field in which the advance has only been secondary to that of joint surgery is in the treatment of gunshot wounds and infections of the chest. Nothing so much lowers the mortality rate and the percentage of infections in gunshot wounds of the chest as the early débridement and closure of the pleural cavity in all sucking wounds of the chest. Few of the cases of perforating wound, or small penetrating wound, where there was no sucking of air into the pleural cavity with each respiration, were subjected to operation unless subsequent infection of the hemothorax occurred, and in my experience it was surprising to see how small a proportion of the cases of hemothorax became infected. There was a definite practice in our own service that any wound of the chest that was operated upon should not be drained, but the wound completely closed. It must be admitted that a small percentage of these cases broke down or became infected later.

Probably the greatest improvement in the treatment of infections of the pleura we owe largely to Depage, who suggested and practised the sterilization of the pleural cavity by constant irrigation with Dakin's solution. Many of you are familiar with the findings of the Empyema Commission in our camps in this country, and the reading of these reports should be sufficient to convince any doubter of the efficacy of Dakin's solution as a sterilizing agent. If there is an area in the body in which infection is tenacious it is the pleural cavity. These infected cavities can be readily sterilized and the chest wall closed, or allowed to close, with absolute disregard of the

cavity itself. Tuffier and Depage have both shown, and hundreds of others have confirmed the observation, that if the cavity is sterile it will remain closed and the lung will expand. This, then, must be our practice in civil life in the treatment of empyema, and when one remembers the prolonged suppuration in these cases and the difficulty of obliterating the cavities by various plastic operations, one must admit that here again we are indebted to military surgery for a great advance.

Gas gangrene early in the war became a formidable enemy and continued so to the end. The gas bacillus was the *bête noir* of the surgeon; it was the cause of more amputations and more deaths than any other organism. Early and complete débridement was the surest means of avoiding the gas infections, but, as this was often impossible, gas gangrene remained prevalent up to the end of the war. Bull's serum was used quite extensively in some of our hospitals, and I believe in some cases it arrested the infection; but in others it had no effect, and in a few the reaction was so severe that it was thought to have hastened an inevitably fatal termination. I cannot speak of its efficiency as a prophylactic agent, though in the latter months of the war I believe it was used quite extensively in the French and British Armies.

An old enemy of the military surgeon, the tetanus bacillus, certainly cut no figure excepting in the early months of the war; that is to say, it was practically wiped out after the use of the prophylactic injections was regularly enforced. I consider it rather remarkable that during the nineteen months spent constantly in surgical work I saw only two cases of tetanus, and neither of these occurred, in the American service. In the early days of the war the French surgeons saw a good many cases of tetanus, but in recent years, with the prophylactic injections in every case of wound, it certainly became the rarest of all infections. One of the two cases I did see occurred in a poor Tommy who was brought into a British clearing station after fourteen days in No Man's Land, and he, of course, did not have the prophylactic injection. This was one of the most pathetic cases that I encountered, and it illustrates, if illustration is needed, that this has been a war in which, owing to the brutality of our enemy, chivalry and humanity were conspicuously absent. Such a thing as a temporary truce for the removal of the wounded was unheard of. This poor man, to whom I have just referred, in spite of an infected wound of the buttock containing clothing, dragged himself from one shell hole to another for fourteen days, living on the food and water which he found on the dead. The most pathetic feature of his case was the fact that although the infected wound of his buttock was being well taken care of and the infection well walled off, he succumbed the day after admission in the agony of tetanic convulsions.

Although we cannot say on reviewing our experiences what th

great Ambrose Paré said after recounting his achievements that "There is nothing left for posterity to discover," or of ourselves what Job said of his comforters, "No doubt that wisdom will die with you," yet there can be no doubt that surgery has made strides in certain directions, and that at least some good has come out of this great evil from which the world has suffered during the past four and a half years.

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### **SOME CLINICAL MANIFESTATIONS OF INFLUENZA IN CHILDREN.<sup>1</sup>**

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THE influenza epidemic of 1918, as it affected New York last fall, cannot be regarded otherwise than as a veritable plague. Nothing like it has been experienced by this generation. The poliomyelitis epidemic of 1916 seems almost insignificant by comparison. Previous epidemics of la grippe we have had ever since 1899, but nothing comparable to this scourge. The disease behaved so differently from any other epidemic that it seems difficult to believe it due to the same microorganism. The pathological findings, moreover, were in many ways very different from those found in other la grippe epidemics.

Two features especially stand out with regard to this epidemic: (1) The wide prevalence of the disease throughout all classes and ages, and (2) the great number and the exceedingly high mortality of the cases with pulmonary complications. Early in the epidemic it was frequently stated that infants and young children escaped the disease, but this was distinctly not true. It was true that the mortality among children was very low compared to that among young adults, and especially as compared to that among pregnant women. But children of all ages were stricken with the disease, and, as will be shown later, pneumonia and bronchopneumonia were the common and often fatal complications in all the severe cases.

As to the wide prevalence of the disease among children, I may note that at Bellevue the Children's Medical Division has 140 beds; during the epidemic in October, November and December, 1918, our daily census rose to between 300 and 360, the rise all due to cases of what we must regard as influenza. At times we had as many as 60 admissions per day, and frequently several children of a family would all come in at one time. I recall distinctly one family of seven and another of eleven including adults, who came to the

<sup>1</sup> Read before the Section on Pediatrics, New York Academy of Medicine, March 13, 1919.

hospital on the same day, two ambulances being required to bring or ~~of~~ them all. At times the social workers or policeman on the block would ~~and~~ every person in the household or flat ill with the disease, no one ~~was~~ being well enough to go out. In other instances the adults and older ~~as~~ children would be ill, leaving no one to care for the smaller children, ~~the~~ so we had many well children brought in along with the sick children and adults. Of course, separate provision had to be made for taking care of these well babies.

Physicians in the tenement districts reported there was barely a ~~the~~ flat without the disease, whole families being stricken almost simultaneously. One doctor reported that he had made fifty calls in one block on one day, and that he had to refuse more for lack of time.

During the months of October, November and December, 1918, we treated in the Bellevue Children's Medical Division over 900 cases due to the epidemic. The great majority of these patients were not very sick, having only a moderate fever after the first day, with symptoms in the upper respiratory tract or pharynx. A large number had severe tracheitis. Only about 10 per cent. had pneumonia or bronchopneumonia, and of these about half proved fatal, the mortality being nearly all in the cases of bronchopneumonia. It was noted especially that when the children belonged to families in which the adults had pneumonia the cases were much more severe and liable to be fatal, so that in many instances whole families were entirely wiped out or only one or two of the younger children left. In this connection a possible explanation of the generally lower mortality among children is that the children are put to bed at once when they have a little fever or do not feel well. They therefore get the great advantage of bed rest from the outset. Older children and adults try to "fight the disease," so to speak, and, like walking cases of typhoid, these patients suffer more severely.

The cases met with may be divided into several main divisions:

1. *Those with High Fever and Prostration but without Physical Signs of any Localization.* These cases are often very puzzling, especially if the temperature continues more than two or three days. The fever is liable to vary widely between morning and evening, ranging from 100° in the morning to 103° or even as high as 106° in the afternoon; occasionally the temperature may fall to as low as 96° within a few hours. When the temperature is high the patients are badly prostrated, showing signs of general toxemia; but when the temperature is normal, or nearly so, they are bright, have a good appetite and digestion and seem hardly sick. Often after the first few days, even when the temperature is high, the child will show no evidences of the fever in the way of fretfulness, drowsiness or prostration.

2. *Cases with Rhinitis or Pharyngitis, or Both.* The greatest number of patients seen at Bellevue were of this type, numbering more than half the cases. The pharynx is red and glazed, often with

the lymph follicles on the posterior pharyngeal wall red and swollen. It is surprising how slight an amount of pharyngitis can apparently be the cause of high temperatures in young children and infants. This is so even without the presence of swollen tonsils. When the tonsils are swollen there is likely to be, after one or two days, swelling of the adjacent cervical glands, and the fever will persist until after the swelling, not only of the tonsils but of the cervical lymph nodes has entirely disappeared. Acute follicular tonsillitis alone was very seldom seen.

3. *Cases with Tracheitis and Laryngitis.* A very important group of patients were those that suffered from inflammation of the trachea or of the trachea and larynx. Tracheitis was far more frequent than laryngitis and was frequently combined either with rhinitis or with bronchitis. A characteristic symptom is the loud, barking cough which is almost incessant, and in younger children it is frequently so severe as to be accompanied or followed by spasm of the larynx. The crowing inspiration, together with the cough, frequently suggests whooping-cough, and is undoubtedly due to the same mechanical condition that produces the cough in that disease, namely, a mass of tenacious mucus at the lower part of the trache. Efforts to dislodge this by the cough are accompanied by contraction of the larynx, and often result in a cramp which is followed by the whoop of the next inspiration. Dr. Wollstein has shown by studies made at the Babies' Hospital some years ago that the influenza bacillus produces a severe tracheitis, resulting in just this form of spasmodic cough, frequently accompanied by a whoop. For these patients, of whom there were a large number, the most satisfactory treatment was to put them in a room in which there was a constant vapor of steam with creosote. To each quart of water in a croup kettle 30 drops of creosote were added, and this was kept boiling constantly. Dry air, either cold or warm, was found to aggravate the cough, and this was especially so if the dry air was cold.

4. *Cases with Bronchitis.* There is nothing peculiar about the bronchitis cases except that the smaller tubes are more liable to be involved, and there is commonly associated some inflammation of the upper respiratory tract, especially the trachea. Moreover, the severe cases are likely to develop into bronchopneumonia.

5. *Cases with Pneumonia.* Only about 10 per cent. of the cases had pneumonia. About four-fifths of the cases with lung involvement took the form of bronchopneumonia. This is in very strong contrast to what usually obtains in pneumonia in infants and children in whom the prevailing type in more than half the cases is lobar pneumonia.

The bronchopneumonia is peculiar in that the signs develop very slowly and irregularly except in those cases that are overwhelmed by the disease. Then both lungs, front and back, are filled with fine rales, especially the lower lobes behind. The consolidation is

patchy and the signs appear irregularly. Frequently the patches increase in size, so that they coalesce to involve the whole lobe. From the manner of development it is clear that the massive consolidation in these cases is due to confluence of the lobular pneumonia and is not a true lobar pneumonia. Commonly there are areas of dulness and bronchial breathing in two or more lobes, or else what indicates the same thing, patches of very fine rales in the midst of larger rales. Pleuritic crepitations are found in the bronchopneumonia of influenza far more often than in ordinary bronchopneumonia. Moreover, empyema occurred in five of the cases, an unusual complication in ordinary bronchopneumonia. The more frequent occurrence of pleurisy with its friction rales causes the signs of lung involvement to last for a longer period during convalescence than we usually find them.

Cyanosis was present in only the severest cases of capillary bronchitis and bronchopneumonia, but the spectrum of the blood failed to show methemoglobin in the only marked case we investigated. The occurrence of cyanosis is not frequent in children suffering from influenza pneumonia, in contrast to what prevails with adults.

The most peculiar feature of bronchopneumonia cases was the occurrence in six instances of interstitial emphysema. Appearing first above or below the clavicles it extended to the thorax, the arm and the back, in two cases down as far as the nipple and in one instance down the trunk and as far as the middle of the thigh, the crepitations being felt throughout the entire area. Apparently the symptom occurs in only the severest cases, for five out of the six died. One child, a boy, aged three years, seemed to be in good condition when the emphysema first appeared in the neck, and it was thought both from the few signs in the lung as well as in the heart action and from his good general condition that he would recover. However, the child succumbed on the third day. In the last case, the patient with double bronchopneumonia of rather chronic course, emphysema appeared all along the right side of the neck and thorax. By means of overlapping rubber adhesive straps, that side of the chest was put at rest and the emphysema gradually disappeared. This child recovered. Perhaps he would have survived without the strapping, but it seemed rational to prevent movement of that lung with further increase of the emphysema.

Just how this interstitial emphysema develops is an interesting and puzzling question. Either the air must pass into the cellular planes of the neck from the mediastinum through a rupture of the bronchi or air vesicles in that region or else it must pass through the adhesions of the two pleural layers, visceral and parietal, in the region of the apex; for in none of these cases was there air in the pleural cavity to form a pneumothorax.

I have asked Dr. Symmers, the chief pathologist at Bellevue.

about his findings at the autopsies, and he tells me that in only one instance was he able to determine the site where the rupture in the lung took place. In this case the air broke through the left lung near the mediastinum and then extended backward behind the pericardium into the cellular planes of the neck. In another instance it was probable that the rupture was in the region of the apex of the lung, but the exact site was not determined. In several cases a pneumothorax resulted from rupture of the visceral pleura and passage of air into the pleural cavity.

As sequelæ of the bronchopneumonia there is frequently some thickening of the bronchi or intra-alveolar infiltration as determined by the roentgen-ray plate. This leads to the radiographic diagnosis of pulmonary tuberculosis, but in two cases I have been able to follow, roentgen-ray plates taken after three months have shown a return to normal lung shadows.

In the matter of blood counts there are great variations. I have met some with a low leukocyte count, with low polynuclears and some cases with a high total and polynuclear count. The variation in the counts probably depends upon the complicating pharyngitis or bronchitis. It is not true that the influenza of children is characterized by a leukopenia, as that of adults seems to be.

The tachycardia that follows the disease has been noted by everyone who has followed the severe cases, and the older children require more care after an attack of influenza than the younger ones. This is because the small child has a large heart in comparison to the size of his body, and as he grows larger the heart gradually becomes smaller in proportion. Relaxation murmurs and excitable heart action may persist for a long time during convalescence.

The gastro-intestinal tract is seldom involved in the inflammation. In two cases, however, there was bloody dysentery, with much blood in the stools. The kidneys are not especially involved.

Very noteworthy in this epidemic as compared to former ones was the infrequency of otitis media and of influenza meningitis. Only a very small number of the patients, even those with marked involvement of the pharynx and tonsils, suffered sufficient inflammation of the middle ear to require paracentesis. In previous epidemics otitis was a very common complication. Absence of influenza meningitis was also very notable. In no instance was this condition found, although meningitis occurred in three cases. In all of these, however, the meningococcus was the causative organism.

**TREATMENT.** With regard to the treatment of influenza there is nothing specific to combat the disease directly. Even for prophylaxis, vaccines, from which so much was hoped and for which great claims were made, do not seem to have brought about results that are definitely advantageous. For the general treatment of the disease the most important thing is rest in bed from the very beginning until convalescence is well established, the patient not



being allowed out of bed until after four or five days of normal afternoon temperature. In my experience the next most efficacious measure is the hot tub bath, repeated two or three times during the twenty-four hours. The temperature of the bath should be  $2^{\circ}$  or  $3^{\circ}$  below that of the patient, and the body should be thoroughly rubbed during a period of from five to ten minutes while the patient is in the tub.

For the catarrhal inflammations of the upper respiratory tract, and especially for the severe cough of tracheitis, for the laryngitis and for the spasmodic contraction of the bronchi, so frequently present in bronchitis, steam inhalations, with the addition of creosote are of the greatest help.

Patients with bronchopneumonia who have nasal obstruction or mouth breathing from dyspnea fare much better in an atmosphere of warm moist air than by the cold-air treatment. It is only after nasal breathing is easy and satisfactory, and after all spasmodic contractions are overcome, that the cold-air treatment is of benefit. For cases of lobar pneumonia without mouth breathing the cold-air treatment is of advantage from the outset. In all cases of capillary bronchitis and bronchopneumonia, and in many cases of lobar pneumonia, the early use of digitalis is of distinct advantage even if the administration is given for only twenty-four hours at the outset. This digitalization of the heart early in the disease permits of a more effective use of the digitalis later, should the need for it arise.

The course of the disease is very uncertain, and relapses and reinfections of different systems are not at all infrequent. It is therefore necessary to make careful examination of the throat, ears and lungs each time the patient is seen unless the temperature is absolutely normal.

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### **PRIMARY CARCINOMA OF THE VERMIFORM APPENDIX: A REVIEW OF THE LITERATURE, WITH A REPORT OF TWO NEW CASES.**

BY EDWARD E. H. BOYER, B.Sc., M.Sc.,  
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(From the Clinical-pathological Laboratory of J. J. Coons, B.S., M.D., and  
H. M. Brundage, M.D.)

BEFORE considering previous cases I desire to present the following case reports:

**CASE I.—History.** Miss M. G., aged twenty-six years, was admitted to Mt. Carmel Hospital on May 22, 1917. Service of Dr. C. S. Hamilton.

*Complaint.* Attack of pain in the midabdomen two weeks previously.

*Personal History.* Negative except pain in the side. Tonsillectomy about four years ago. Menstrual history negative.

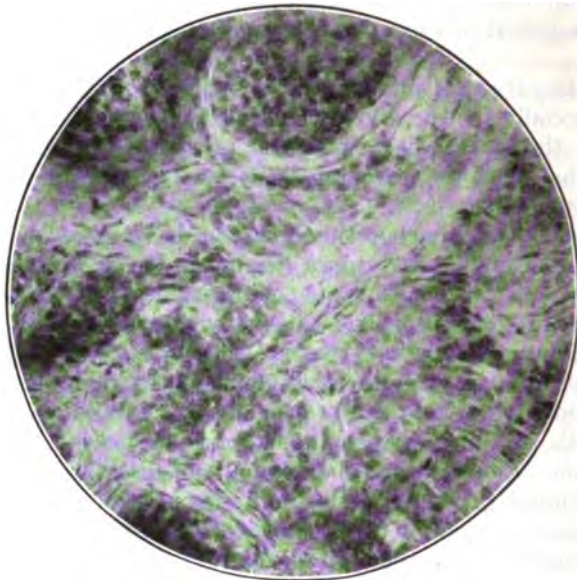


FIG. 1.—Case I. High-power photomicrograph.

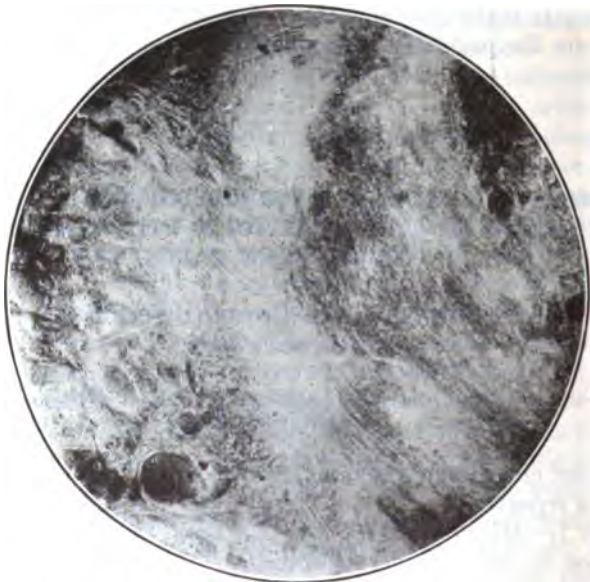


FIG. 2.—Case I. Low-power photomicrograph.

*Present Illness.* Has had attacks varying in frequency, several per year, for the last ten years. Has never been nauseated or vomited during any of these attacks, nor were the attacks severe enough to place patient in bed. Hypodermic injections were required to allay the pain. No movement of bowels during the attacks.

*Physical Examination.* Head and neck negative. Heart and lungs normal. Abdomen: no tenderness or discomfort at time of examination.

*Operative.* Incision rather high. Tremendous enteroptosis. Normal gall-bladder and kidney. Typical chronic appendix, reduced in size, irregular in shape and thickened, containing concretions. Appendectomy was performed. The patient made an uninterrupted recovery and left the hospital two weeks later.

*Pathological Report.* Gross appearance. The appendix is 5 cm. long, 7 mm. in diameter at the proximal third and 9 mm. through the distal portion. There are no adhesions and nothing suggestive of malignant growth. The lumen of the proximal portion is patent and contains fecal concretions. The lumen of the distal portion is obliterated by a fibrous growth. The wall of the distal portion is thickened to about 3 mm.

*Microscopic Appearance.* Section through the proximal portion shows the mucous membrane intact. The lymph nodes are slightly enlarged and the mucosa and submucosa are infiltrated with lymphoid cells. The muscular coats show a similar but less marked infiltration. There is no suppuration. The serosa is normal. The picture is one of a mild diffuse appendicitis.

Section through the distal portion exhibits an entirely different picture. The lumen is entirely obliterated by a mass of fibrous tissue. Scattered throughout this mass are numerous alveoli of epithelial cells. The alveoli vary in size and shape and contain from 4 to 200 or more cells. These cell nests show no apparent central degeneration or necrosis. Single epithelial cells are distributed diffusely and there is a slight infiltration of lymphoid cells. The mucous membrane is entirely absent. There is a submucosa, the fibrous nature of which is largely replaced by the epithelial cells of the new growth. No lymph nodes are seen. The muscular coats, especially the outer longitudinal layer, are infiltrated by a dense mass of epithelial cells, arranged singly and in alveoli. The new growth seems to have penetrated in all directions, but stopped short at the serosa. The epithelial cells throughout the entire section are of the spheroidal type. A few mitotic figures are found. It is impossible to locate the starting-point of the neoplasm.

*Diagnosis.* Spheroidal-cell carcinoma.

CASE II.—*History.* Miss N. H., aged thirty years, was admitted to Mt. Carmel Hospital on July 18, 1918. Service of Dr. C. S. Hamilton.

*Complaint.* Pain in the side for many years. Acute pain at time of admission.

did not close such a wound was open to the criticism of not doing up-to-date surgery. The results warrant the change in practice, for drainage invariably meant infection of a more or less serious nature and infection meant more or less incapacitating ankylosis or even worse. I have seen a straight series of ten gunshot wounds of the knee-joint, with fracture in all but one, treated by four surgeons (Pool, McWilliams, Jopson and Heuer) at Evacuation Hospital No. 1, heal by primary union and the patients leave the hospital with movable joints. And still can anyone doubt that surgery has advanced since and as a result of the war?

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to the anterior border of the trapezius muscle. This edematous area is rather sensitive to pressure, but it does not pit and is not of a hard consistency.

Owing to the suspicious character of the pustule, smears and cultures were taken from the red indolent ulcerative surface by lifting up the margin of the eschar.

November 24. As the smears and cultures of the previous day seemed suspicious of anthrax, smears and cultures were again taken, the latter in nutrient broth and on several Petri dishes of blood-agar. A specimen of blood was taken for cultural purposes. At 10 A.M. 48 c.c. of anthrax serum were injected intramuscular in the right buttock. In the evening 10 c.c. of serum were injected into the indurated tissues immediately around the pustule. From 99° at 8 A.M. the temperature rose to 101° at 8 P.M. By 8 A.M. the following morning the temperature had fallen to 99° again. Evidently the febrile excursion was part of a serum reaction.

November 25. The patient's general condition remained good, but he was drowsy. There was considerable acute tenderness and a slight extension of the edema in the region of the pustule, and the lesion seemed more definitely elevated above the surrounding tissues. Another injection of 30 c.c. of anthrax serum into the right buttock and 10 c.c. of serum into the region around the lesion were given.

November 26. The inflammation and swelling around the lesion were quite marked in the early part of the day, but subsided rapidly by evening, leaving the indurated tissues about the pustule somewhat reduced in size.

November 27. The pustule has now shrunk considerably and has lost its red areola, but it stands out more prominently from the underlying tissues, owing to the fact that the induration of the surrounding tissues is much less. The most marked swelling is now localized to a mass of glands situated just below the angle of the jaw. Twelve cubic centimeters of serum were injected into the immediate region of these enlarged glands.

November 29. Another intramuscular injection of 30 c.c. of serum was given. Glandular swelling subsided rapidly.

November 30. Patient continues to improve clinically. Is somewhat drowsy after serum. The pustule is subsiding rapidly, apparently melting away.

December 2. Progress continues satisfactorily. There is slight soreness and swelling around the area of swollen glands in which the serum was injected. The lesion is now only a raw ulcerated surface even with the adjacent skin. Patient has several rather superficial abscesses scattered over the body. Incision and drainage of one on forearm. Cultures were taken.

December 12. Patient has lost quite a little weight since admission, but he feels well and has been up and around for the past

week. The lesion has now dried up, leaving a thick and very adherent crust, resembling in every respect a piece of burnt leather. This crust was removed, but only with great difficulty, as it was extremely adherent, and cultures were taken from its under surface, from the ulcerated raw surfaces beneath and from the seropurulent discharge which could be pressed from the lower part of the pustule.

December 14. Today the crust has reformed at the lower part of the wound. The rest of the lesion is even and smooth with the skin, not unlike a vaccination scar, but not so much depressed below the surface. A serous discharge was pressed from the lower margin of the wound after the crust was removed. This was cultured. Tincture of iodine was used locally to dry the pustule.

December 18. Patient feeling very well and lesion healed.

December 20. Discharged, apparently cured.

February 15, 1919. Patient again seen and examined. His health is excellent and there are no evidences of any detrimental effect of his recent attack of anthrax. At the site of the local lesion there remains nothing but a small circular scar, about the size of a dime, a little depressed below the surrounding skin.

*Pathological and Bacteriological Findings. Blood Culture.* Taken November 24, remained sterile. Evidently there was no blood infection.

*Blood Counts.* December 2. Total leukocytes, 19,600; polynuclears, 78 per cent; lymphocytes, 22 per cent.

December 4. Total leukocytes, 13,300; polynuclears, 72 per cent.; lymphocytes, 26 per cent.; eosinophiles, 2 per cent.; total erythrocytes, 5,680,000.

*Urine Examination.* November 25. Albumin, very faint trace; Fehling's, negative; reaction acid; specific gravity, 1030; occasional hyalin and granular cast. Culture and smears were made from centrifuged specimen, but the bacteriological examination was negative.

*Smears and Cultures from Pustules.* November 23. Direct smears showed pus cells, staphylococci and a fair number of bacilli; Gram-positive; long, square end and rough in outline.

Culture on agar plate in twenty-four hours showed many opaque grayish-yellow colonies, 1 to 2 mm., several 4 to 5 mm. dry, opaque, white, with scalloped borders. Microscopically the small colonies proved to be staphylococci; the large colonies were found to be composed of Gram-positive bacilli; large, square end, single and in chains. A hanging drop showed the bacilli to be non-motile.

Large anthrax colonies transplanted to plain agar for further study.

November 24. Broth culture: The broth is cloudy. Examination microscopically shows numerous staphylococci and a few larger Gram-positive bacilli square end and non-motile.

November 25. Transplant colonies on plain agar have now

developed. They are dry, opaque and have fringing projections. On low magnification these colonies seem to resemble a head of hair. Smears from the colonies show the same large Gram-positive bacillus previously found. It is non-motile after several days. Other smears contained long chains of bacilli, showing spores of an elliptical shape, one in each bacilli.

November 24. Six more smears made from the pustule, stained by Gram and examined, showed pus cells, numerous staphylococci and a Gram-positive bacillus. Three more agar plates were inoculated from the pustule.

November 25. First plate: Colonies—many opaque, white, 1 to 2 mm. and some large, flat, opaque, dry, with fringes from the borders. Low magnification shows Medusa-head appearance, so typical of anthrax. Second and third plate showed same appearance.

Microscopic examination of smears from all three plates showed numerous staphylococci and many large Gram-positive square-end bacilli, single and in chain formation; non-motile.

Transplants made to broth, and the following day examination showed a dense sediment at the bottom of the tube, with the supernatant fluid clear. Hanging drop shows a non-motile bacillus.

Transplants made to gelatin, and examination made the following day showed white opaque colonies; at the end of two days the gelatin was completely liquefied.

Transplants made to agar for animal inoculation. In making transplants, material was taken from the fringes and was found to be pure. In one or two instances staphylococci colonies were found in the center of the large anthrax colonies, but the anthrax grew pure at the border.

*Animal Inoculation from Cultures of the Pustules.* Mouse No. 1. November 27, 7 P.M. An emulsion was made in broth of the pure growth obtained on agar. Then 10 drops of this emulsion were injected into the mouse at the root of the tail, the area of injection being sterilized by alcohol. The animal was in fair condition until 10 A.M. the following day, when it suddenly died.

*Necropsy.* At the point of inoculation there is an indurated and rather edematous area. On incision this induration is found to be composed of a glairy and rather gelatinous exudate. The neighboring lymph glands are enlarged and ecchymotic. No change was visible microscopically in the internal organs. Cultures were made on plain agar plates from the heart, liver, kidneys and spleen.

November 29. Cultures from the internal organs of the mouse were examined.

Liver: Many colonies +++; dry, white and opaque. Microscopic examination shows anthrax bacilli; non-motile.

Heart Blood: Many colonies ++++; dry, white and opaque, as above. Microscopic: Anthrax bacilli.

Kidney: Colonies ++++, same appearance. Microscopic examination shows anthrax bacilli.

Point of Inoculation: Gelatinous exudate; colonies +++++; same appearance.

The plates from these organs were kept for several days and preserved the appearance of anthrax colonies. The bacilli exhibited spore formation and a capsule was definitely demonstrated.

*Cultures from the Shaving Brush of the Patient.* The patient used the brush for the first time when he cut himself in the spot in which the pustule subsequently developed.

November 25. Agar plate shows many opaque, moist small to large-sized colonies. Also a few large, dry, flat opaque-like anthrax. Microscopic examination of smears from these colonies showed many cocci, both Gram-positive and negative. Many bacilli, short and long, some thick and some slender. Some of the bacilli resembled those obtained from the pustule. Transplants were made from the large, dry, flat colonies for further study.

November 26. Subcultures show colonies of one type, namely, dry, flat, opaque, with fringing borders. On low magnification these are thick and white, the fringes being more transparent.

Microscopic examination of smears made from the colonies show them to be composed of Gram-positive bacilli, long, thick, square end, single or in chains, and non-motile. After several days spores appeared in the filaments.

Transplants made to broth and gelatin from the subculture on agar plates.

Broth: After one day a sediment appeared in the bottom of the tube. The supernatant fluid was clear.

Gelatin: White colonies appeared and in two days the gelatin was completely liquefied. The appearance of the colonies is identical with those from the pustule, and liquefaction proceeds at the same rate.

There are then no differences to be observed between the organism from the pustule and that from the brush as to colonies, microscopic appearance, spore formation and motility. It now remained only to inoculate a mouse to prove them identical.

*Animal Inoculation on Mouse No. 2.* December 2. The mouse was inoculated with an emulsion of anthrax colonies obtained from cultures of the shaving brush. About 10 minims of the emulsion were injected at the root of the tail. The mouse was fairly well for about ten hours, and then died suddenly.

*Necropsy.* Soft swelling at the point of inoculation. Internal organs seemed normal macroscopically except the spleen, which was enlarged. Direct smears and cultures were taken from the heart, lungs, liver, kidney, spleen and gelatinous edema.

Examination of Smears. In all there was found many anthrax bacilli. A fair number of the bacilli had a capsule. The form was often quite irregular. The ends frequently appeared bent like a hook. A few spores were present in the bacilli from the gelatinous edema.

**Cultures.** The growths on most of the plates, as those from the heart, liver and kidney, were pure anthrax, but on some of them there was also a slimy growth which proved to be a small Gram-negative bacillus, evidently a contamination from the skin of the mouse (normally a small Gram-negative bacillus lives as a saprophyte in the skin of the animal).

*Subsequent Smears and Cultures from Pustule.* December 4. A plate culture on agar was taken from the lesion. It showed only staphylococci.

December 14 Two other plate cultures on agar showed only staphylococci. Direct smears from the lesions showed pus cells and staphylococci.

December 4. Cultures from abscesses on the arm showed staphylococci.

**RESUMÉ.** 1. The definite history of the manner in which the disease was contracted—accidental cut during shaving and the use of an infected shaving brush.

2. The mildness of the attack, despite the situation of the malignant pustule in the neck.

3. The subsidence of the local and constitutional symptoms without excision of the lesion.

4. The apparent benefit of the intramuscular injection of anthrax serum.

5. The definite improvement in the pustule itself following the injection of anthrax serum into the indurated tissues of the neck surrounding the lesion. This local use of serum we believe is one of the prime essentials for the successful treatment of anthrax.

6. The absence of a blood invasion.

7. The recovery of the anthrax bacillus on several different occasions from the pustule, both by smears and cultures.

8. The absolute proof of its identity as anthrax by its morphology, its cultural characteristics, the effect in producing death on inoculation of cultures into mice and finally the recovery of the bacillus in pure culture from the animal. (The morphology of the organism in smears from the pustule is not enough to identify it. Its lack of motility and the fact that it possesses a capsule must be proved to differentiate it from the *Bacillus subtilis* and the bacillus of malignant edema.)

9. The recovery of the organism from the shaving brush of the patient. The similarity of this bacillus in its morphology, cultural characteristics and results upon animal inoculation to that which was found in the malignant pustule.

The writers take this opportunity to thank Mrs. B. Riehl, of the Laboratory Staff of the Hospital, for her valuable assistance in connection with the laboratory work upon the case.

**THE METHOD OF OBTAINING CEREBROSPINAL FLUID  
BY PUNCTURE OF THE CISTERNA MAGNA  
(CISTERN PUNCTURE).**

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IN conducting the early experiments on the physiology and chemistry of the cerebrospinal fluid, two routes for securing the fluid from animals were employed. The first of these was the lumbar and the other was that afforded by the space between the occipital bone and the first cervical vertebra, a position which recommended itself, since at this point no bony obstruction interferes with the approach to the subarachnoid space, the opening here being covered by the occipito-atlantoid ligament. Both routes were utilized, however, only after a preliminary operation was performed; in the lumbar region the spinal membranes were exposed by laminectomy, and in the cervical position the ligament was bared by a median incision through the structures of the back of the neck. Such procedures, while they served their purpose well for acute experiments, made it difficult to conduct observations over a prolonged period. In 1890 Quincke demonstrated that the lumbar fluid spaces could be reached by direct puncture, and so placed in the hands of clinicians a valuable method for obtaining human spinal fluid for analysis. Unfortunately the ease of withdrawing lumbar spinal fluid in man does not apply to laboratory animals when the intervertebral spaces are narrow and very oblique. Because of this anatomical arrangement, experimentalists continued for some time, subsequent to Quincke's demonstration, to experience difficulties in securing specimens for study without resorting to the annoying feature of preliminary operation. Dixon and Halliburton,<sup>6</sup> in 1913, showed that the cerebrospinal fluid reservoirs of a dog could be reached successfully by a direct puncture through the occipito-atlantoid ligament. This method has since been used extensively by Weed,<sup>14</sup> and in the Army Neurosurgical Laboratory, under his direction, it has been relied upon almost entirely for the exploration of the subarachnoid space.

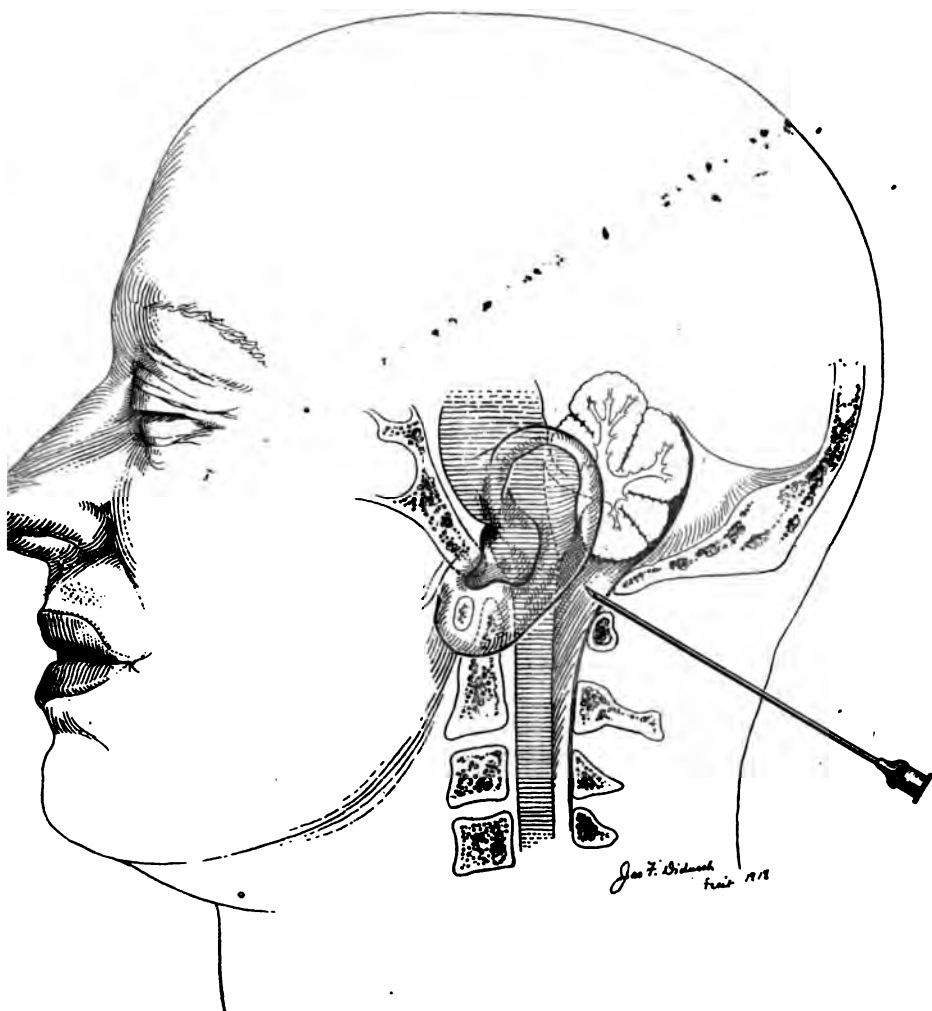
The technic for performing occipito-atlantoid puncture in animals is quite simple, and, after a little practice, not much difficulty is encountered in securing perfectly clear normal fluid. To locate the

occipito-atlantoid ligament in the cat the thumb is placed in the depression situated below the occipital protuberance and limited laterally by the superior nuchal lines. By manipulation of the head a definite soft spot may be felt at the lowest part of this depression, just above the spine of the axis. This area corresponds to the interruption in bony continuity between the base of the skull and the spine. The fluid reservoir lying just below the ligament constitutes the lower part of the cisterna cerebellomedullaris, and it has at this level in the cat a depth of about 5 mm., representing the distance between the inner surface of the ligament and the posterior surface of the cord. The nervous structures at the level of the ligament constitute the transition between the spinal cord and the medulla, so that care must be taken not to advance the needle too far in performing the puncture. The space afforded by the cistern is quite sufficient, even in such small laboratory animals as the rabbit, guinea-pig and even the rat, to permit repeated punctures in this area without causing injury to the nervous tissue. Observance of the following points in technic have been of service in performing the operation in this laboratory. The instrument found to be most satisfactory is an 18-gauge lumbar puncture needle cut down to about 5 cm. The point must be sharp, but the bevel should not exceed 2 mm. The skin is pierced in the midline just above the spine of the axis, but before proceeding further the subcutaneous tissue should be freed from the point of the needle to prevent its deflection during the next steps of the procedure. The head of the animal is then firmly grasped in the left hand, the thumb resting in the depression below the occipital protuberance. Using the left thumb as a guide, and with the head well flexed, the needle is carried carefully into the cistern. The direction must be slightly upward rather than perpendicular to the skin, so that the needle will be directed obliquely to the cord and medulla and further advance will carry it higher into the cistern rather than into the nervous structures. As soon as resistance ceases to be felt the operation is complete and removal of the obturator should be followed by the appearance of cerebrospinal fluid. Sometimes on removing the obturator, however, pure blood will issue from the needle. In such cases it will be found that the puncture has been made too near the edge of the ligament, and one of the suboccipital veins in the neighborhood has been entered. Usually in such cases the needle has not entered the subarachnoid space and a second attempt with a fresh instrument will yield clear fluid.

An analysis of 1186 punctures of the occipito-atlantoid ligament done on cats in this laboratory showed that an injury of the medulla was occasioned only ten times (0.84 per cent.). By a further analysis of these figures it was found that seven of the accidents occurred during the early months of the work, and among the last 527 punctures similar injuries were made only three times. Several



of these were brought about by attempts to obtain fluid for analysis from animals which had been given a purulent meningitis. In these early experiments it was not realized how very thick and viscid the spinal fluid could become in a cat, and when a flow did not follow



Topographical study to show the landmarks used in performing cistern puncture. Composite prepared from numerous tracings of frozen sections. One-half actual size.

the removal of the obturator from the needle the technic was blamed and further prodding in the attempt to locate a pocket of fluid would end occasionally by injury of the medulla. When puncture has been properly performed and no fluid obtained it was subse-

quently found in thirty-five dry taps that failure was due to lack of fluid, increase in its viscosity or to adhesions, and not to faulty technic. Consequently, in later experiments such cases were not further explored. The presence of a small amount of blood cannot be avoided in all cases, but of the fluids obtained 69 per cent. were free from red elements, a proportion which could be greatly increased by considering the recent cases only.

The method has proved so satisfactory in the laboratory and so safe in experienced hands that it was thought advisable to investigate the possibility of its use clinically. Accordingly, investigations were undertaken on cadavers with the object of determining the anatomical relations in the human subject. The accompanying drawing is a composite made from numerous studies of frozen head sections and represents the relations of the structures to be considered in the average subject. The occipito-atlantoid ligament stretches from the posterior rim of the foramen magnum to the corresponding position on the first cervical vertebra. Closely applied to its anterior surface is the dura mater and directly under this meninx lies that portion of the arachnoid membrane which forms part of the posterior wall of the cisterna cerebellomedullaris. The anterior wall of the cistern is formed by the posterior surfaces of the upper cervical cord and the lower part of the medulla. The depth of the fluid reservoir, namely, the distance between the arachnoid and the posterior surfaces of the cord and medulla, is about 1.5 cm. at the level of the occipito-atlantoid ligament. For introducing the needle a point is selected in the midline of the back of the neck just above the spine of the axis. The glabella and the upper edge of the external auditory meatus were found to be valuable structures for directing the course of the needle, for a plane passed through them and the point of insertion on the back of the neck will pass also through the occipito-atlantoid ligament. This relationship has been a constant one in all of the subjects studied and is clearly shown in the illustration. In thin individuals palpation over the back of the neck often reveals a deep depression between the occipital protuberance and the spine of the axis, and with the tip of the finger the approximate position of the occipito-atlantoid ligament can be directly located. The distance necessary to insert the needle in order to reach the cistern varies, of course, with the individual. From a number of measurements taken at the time of puncture on cadavers the average distance was found to be 4 cm., and it rarely exceeded 5 cm. or was less than 3 cm. In view of the uncertainty occasioned by such measurement the operator will find it necessary to rely upon his tactile impressions produced when the point of the needle overcomes the resistance offered by the ligament and dura and passes into the cavity of the cistern. For one skilled in performing lumbar punctures this sensation is quite definite, and for us, in performing the operation both in the clinic and at autopsy, it has given an

infallible index of when the cistern has been reached. After punctures on the cadaver the needle was left in place in several instances and the brain was removed. In this way an idea was obtained concerning the exact position the point of the needle assumed and how far it actually projected into the cistern. Such controls showed that the needle never projected far enough to cause any great anxiety that the medulla would be injured if the operation were carried out in experienced hands. Furthermore, it was learned that the skull could be moved on the occipito-atlantoid articulation in all directions without appreciably altering the relations of the needle point to the nervous structures. These tests were made, for it was felt that the relations between the posterior wall of the cistern and the medulla might be so altered as to cause damage to the nervous system were a patient to give a sudden unexpected movement of the head while the needle was *in situ*; the findings indicate that such movements of the head when the needle is in place would not be dangerous.

When once we had become familiar with the technic it was found that on cadavers the operation was easier than lumbar puncture and that fluid was more readily obtained at this point. It has therefore become our routine practice at the autopsy table, where examination of the cerebrospinal fluid is required, to obtain it by cistern puncture. This, then, is offered as our first use of the method.

In the living, one of the first uses to which this method recommends itself is in cases of spinal subarachnoid block incident to the course of meningitis. The presence of such blocks is manifested usually by the inability of the physician to obtain spinal fluid in the lumbar region, and the occurrence has led, in a number of instances, to the utilization of other routes for reaching the fluid reservoirs. Such complications led Chartier<sup>4</sup> to make the puncture in the eighth dorsal space in two instances, and later a case similar to his induced Ravaut and Krolunitsky<sup>13</sup> to insert the needle between the sixth and seventh cervical vertebrae. Both of these routes were used successfully by Netter.<sup>11</sup> Quincke<sup>12</sup> early suggested that fluid could be obtained from the cisterns by suitable punctures, but considered them impracticable and dangerous for routine practice. Cazamian,<sup>3</sup> however, adopting the sphenoidal route, successfully tapped the basal cisterns by inserting the needle from in front below the eye. The space between the occiput and atlas has been used for drainage of the spinal fluid by Cushing and also by Haynes, but these operators resorted to the open methods of the early experimentalists. In several cases of meningitis in which lumbar puncture failed to yield fluid, Herrick<sup>8</sup> found at autopsy the adhesions preventing the communication between the spinal and cranial subarachnoid spaces to be around the foramen magnum. In one of these he reports an unsuccessful attempt to reach the cistern through the occipito-atlantoid ligament.

The following case, observed on the medical service at Camp Jackson, S. C., is given here through the courtesy of Major W. W. Herrick, and illustrates, in spite of the subsequent fatal issue, the clinical use of the occipito-atlantoid puncture when blockage occurs in the spinal canal. This patient having, under venous and sub-arachnoid serum therapy, apparently recovered from an attack of epidemic meningitis, suffered a relapse one month later. At this time lumbar puncture failed to produce more than 5 c.c. of fluid, and as the man was rapidly becoming worse, an attempt was made to break up the adhesions around the foramen magnum by rotating the head on the spine while the patient was under an anesthetic. This failed to accomplish its purpose and repeated lumbar punctures during the following ten days netted but 5 to 10 c.c. at a time. Although the relief of pressure occasioned by the release of even these small quantities was followed by a transient improvement in his condition at first, he eventually developed a stupor from which it was impossible to arouse him. The patient's condition was so grave that an attempt at least to relieve his condition by occipito-atlantoid puncture was justifiable. Accordingly, he was given a light chloroform anesthesia and the operation performed. The procedure was successful; 40 c.c. of turbid but blood-free fluid were obtained and 25 c.c. of serum injected, following which the patient became conscious and showed marked improvement. About twenty-four hours later (before the procedure could be repeated) death occurred. At autopsy a lumbar puncture yielded a few drops of very yellow amber fluid. In order to demonstrate the suspected block of the spinal canal, 35 c.c. of ink were injected with a syringe into the subarachnoid space through the lumbar needle. Following this a needle was inserted into the cistern and about 10 c.c. of turbid, blood-free fluid showing no traces of ink were aspirated. On exposing the spinal cord the canal was normal and on opening the dura the space beneath was entirely free of exudate. Beneath the arachnoid the ink was found to have stopped abruptly at the level of the sixth thoracic vertebra. The arachnoid was milked from below upward to see if the ink could be forced farther up the cord, but this manipulation resulted merely in ballooning out of the arachnoid at the upper limit of the injection without further upward passage of the ink. Above the line of injection, where the pathology was not obscured by the ink, the subarachnoid space was completely filled with a very thick fibrinous exudate, which in itself would be a marked hindrance to the free passage of the fluid within the membrane. The brain was then removed and examination of the structures in the canal at the level of the occipito-atlantoid articulation showed no evidence of injury by the puncture done the day before and no trace of the ink injected postmortem into the lumbar subarachnoid space.

A recent personal communication from Major Herrick informs us that he has since performed the operation successfully on a patient having streptococcus meningitis.

Another use of the procedure, especially in those cases of septic purulent meningitis other than of meningococcus origin, will be found by combining it with lumbar puncture for instituting an irrigation of the spinal canal. The value of irrigating the canal and thus getting rid of a large part of the pus and debris contained in it during infection has been recognized as a logical surgical procedure by Cushing and Sladen,<sup>8</sup> Aubertin and Chabanier,<sup>1</sup> Capitan<sup>2</sup> and others. These investigators made use of a retrograde lavage, the method being to inject suitable amounts of a bland solution in the lumbar region until the canal was filled. The solution was then permitted to flow off again at the lumbar needle and the process was repeated until the returned fluid was clear. The method has a disadvantage in that during the first injection infected debris may be shoved ahead of the fluid and find lodgment higher up in the canal if not at the base of the brain. Later, Franca<sup>7</sup> and Miller<sup>10</sup> went a step farther and used two needles, one inserted in the lower thoracic and the other in the lumbar region, passing a stream of Ringer's solution between them. We have been able to irrigate living cats from the cistern to the lumbar region and in the opposite direction with ease and for long periods of time; also in the cadaver the procedure has been found quite simple. Early in the summer of 1918 there was referred to us, through the courtesy of Major Joseph C. Bloodgood, a patient in whom the application of the combined occipito-atlantoid and lumbar puncture for a complete irrigation of the spinal meninges might be applied. The case was that of a man who, secondary to a basal fracture, developed a streptococcus meningitis, which at the time he was seen by us had advanced so far that there was little chance of benefiting him much by any procedure. With the patient under light chloroform anesthesia the lumbar and cistern punctures were accomplished without difficulty and the purulent spinal fluid was allowed to flow from both needles until the subarachnoid cavity was fairly well depleted. The upper needle was connected with a reservoir containing warm Ringer's solution, which was introduced into the subarachnoid space under about 100 mm. water-pressure. The flow between the needles was very satisfactory and a great quantity of additional pus was removed by the irrigation, which lasted about five minutes. Unfortunately, the procedure could not be repeated on this patient, who died about twenty-four hours later, but the single experience was useful in demonstrating the feasibility of the operation, and the ease with which the occipito-atlantoid puncture was accomplished recommends its use in similar cases.

With increase in our experience in the use of this method it is

entirely possible that this route should prove of value for the introduction of serum early in epidemic meningitis for the following reasons: The ordinary dosage (25 to 40 c.c.) of serum given at the lumbar region is not sufficient to fill more than the subarachnoid space of the cord, a fact that has been demonstrated in this laboratory by injecting similar doses of detectable suspensions into the lumbar canal of cadavers. In the case of a well-developed adult man, recently dead, such an injection of 30 c.c. of India ink were found to have blackened the entire subarachnoid space of the cord, but to be thinned out over the base and not visible at all over the convolutions. Proportionate doses of the same material were given both by the occipito-atlantoid and the lumbar routes to living cats shortly before they were sacrificed. In these it was found that the spread from the lumbar needle had reached in marked concentration as high as the foramen magnum, but around the base of the brain the ink particles were present only in great dilution. On the other hand the ink injected at the occipito-atlantoid ligament completely filled all of the basilar cisterns and extended well over the convexity of the brain. In accordance with the frequent finding of the earliest lesions of meningitis over the cortex, and because of the fact that serum administered at the lumbar region frequently fails to clear up the infection in the brain, these experiments suggest that an injection of serum given directly into the cistern early in the disease would be of great benefit. Koplik,<sup>9</sup> discussing epidemic cerebrospinal meningitis, emphasizes the tendency in children toward early blockage of the cerebrospinal fluid spaces and hydrocephalus formation, and appeals for some method of administering serum in the meninges other than by lumbar or ventricular punctures.

In conclusion, it may be said that puncture through the occipito-atlantoid ligament offers a convenient method for obtaining cerebrospinal fluid from laboratory animals; it has also been found more satisfactory than lumbar puncture in obtaining fluid at the autopsy table. After study of the anatomical relations of the cisterna in man, and after numerous successful punctures on the cadaver, we believe that the operation in skilled hands is a safe one for clinical use. We do not wish to minimize the possible harm which can result from such puncture; on the other hand, we are convinced that the technic is not difficult and that practice upon the cadaver will be convincing on this point, without which preliminary study the operation should not be performed.

Clinically, the procedure should prove useful (1) in reaching the upper fluid reservoirs of the central nervous system after blockage of the spinal subarachnoid space; (2) in combination with lumbar puncture for irrigation of the spinal subarachnoid space; and (3) in affording a method whereby specific therapy could be given more efficiently in early meningitis.

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## ACUTE HEMATOGENOUS STREPTOCOCCIC PERITONITIS.

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DEFINITION. Acute hematogenous streptococcic peritonitis is the designation used by the writer in cases produced by a streptococcus infecting the peritoneum by way of the blood stream without an apparent intermediary lesion of an abdominal viscus being demonstrable.

PRIMARY PERITONITIS. Authorities are divided as to whether a true primary peritonitis exists. Medical literature is meager in reports. Lewi,<sup>1</sup> Meade,<sup>2</sup> Collie<sup>3</sup> and Semple<sup>4</sup> described several

<sup>1</sup> Tr. Med. Soc. New York, 1873, p. 143.<sup>2</sup> British Med. Jour., 1876, ii, 393.<sup>3</sup> Med. Exam., 1877, ii, 843.<sup>4</sup> Ibid., 1878, iii, 553.

cases and attributed the peritonitis to exposure. Grawitz,<sup>5</sup> in 1886, reported 13 cases of "idiopathic" peritonitis. In 1893 Tavel and Lanz<sup>6</sup> divided the peritonitides into a primary group and other numerous secondary groups classified according to the viscus harboring the causal focus. Flexner,<sup>7</sup> in 1898, simplified the classification by subdividing all secondary cases into an exogenous and endogenous type, depending on whether the infection reached the peritoneum directly from without (*e. g.*, operation, stab wound, lesion of the abdominal wall) or from a lesion of an abdominal organ. The primary cases he attributed to infection carried to the peritoneum through blood or lymph channels.

In 1901 Nothnagel<sup>8</sup> denied the possibility of such an entity as primary peritonitis. In a case in which streptococci were present in the throat and peritoneal exudate, he claimed that the organism had been swallowed with the sputum and wandered out through the intact stomach wall thus reaching the peritoneum. Sheldon<sup>9</sup> believed these cases had their origin in microscopic lesions of the appendix or other abdominal organs. Armstrong<sup>10</sup> insisted on the Fallopian tubes being the seat of the primary infection, because his cases of primary peritonitis all occurred in females. Wilder<sup>11</sup> believed they were secondary to throat lesions. Bond<sup>12</sup> and Jensen<sup>13</sup> maintained that microscopic intestinal lesions could initiate many of these primary cases of peritonitis.

Jensen fed some animals with virulent cultures of pneumococci in capsules. One of the animals died. At the postmortem examination a purulent peritonitis was found. A follicular enteritis with slight necrosis of Peyer's patches was present, but there was no ulcer or perforation. Pneumococci were found in the intestinal canal, intestinal wall, blood and peritoneum. Flexner,<sup>14</sup> in 1895, mentions the finding of diplococci in the lumen of the intestine, mucosa, submucosa and within the peritoneum in certain cases of infection of the intestine. These organisms were also present in lymphatic spaces, which he believed were the avenue of transit into the peritoneal cavity. He,<sup>15</sup> however, stated that while it would be possible for organisms to wander out through the normal intestinal wall, no definite proof of such an occurrence had yet been offered. Flexner believed that in all cases wherein the intestine was responsible a gross pathological lesion was present. Abacoumova<sup>16</sup> reports a case

<sup>5</sup> Charité Ann., 1884, xi, 770.

<sup>6</sup> Mitt. a. klin. u. med. Instituten d. Schweiz, 1893, i, 1.

<sup>7</sup> Philadelphia Med. Jour., 1898, ii, 1019.

<sup>8</sup> Wien. med. Presse, 1901, xlii, 1321.

<sup>9</sup> Med. Rec., New York, 1902, lxii, 394.

<sup>10</sup> Montreal Med. Jour., 1903, xxxii, 728.

<sup>11</sup> Tr. Chicago Path. Soc., 1916, x, 46.

<sup>12</sup> British Med. Jour., 1905, ii, 232.

<sup>13</sup> Arch. f. klin. Chir., 1903, lxxix, 1134; Ibid., lxx, 91.

<sup>14</sup> Bull. Johns Hopkins Hosp., 1895, vi, 64.

<sup>15</sup> Flexner: Loc. cit.

<sup>16</sup> Thèse. de Lausanne, 1905.



in which streptococci were present in the intestinal wall. Lennander's<sup>17</sup> case was one of follicular enteritis.

The theories of gastric or intestinal causation appear disproved by the reports of cases of primary peritonitis in which the causative organism has at an early stage been recovered from the blood. Künzel's<sup>18</sup> case, in which most thorough gross, microscopic and bacteriological studies were made at the postmortem examination, furnishes us with absolute evidence as to the direct infection of the peritoneum by way of the blood stream from the nasopharynx without an intermediary abdominal lesion. Appendix, spleen, intestine, uterus, tubes and ovaries were all normal. On culture these organs proved sterile, or, as in the case of the intestine, yielded no organisms of the streptococcic group. The streptococcus was recovered only in the nasopharynx and peritoneal exudate.

**TYPE OF PRIMARY PERITONITIS.** The type of primary peritonitis mentioned by Flexner, Manahan<sup>19</sup> and Fishbein<sup>20</sup> occurred exclusively as a terminating infection in chronic disease—*e. g.*, valvular defects, chronic parenchymatous nephritis, arteriosclerosis, cirrhosis of the liver and visceral carcinomata. The writer has studied 8 cases of primary peritonitis, all due to the streptococcus, that were entirely of a different character. Seven occurred in females and only one in the male. Their ages ranged between ten months and twenty-one years. They were in the best of health when stricken with this disease. In no instance could the peritonitis be ascribed to a metastatic process in an abdominal organ the result of a septicemia or pyemia. Metastatic foci in abdominal organs are rare in cases of general streptococcic infection.<sup>21</sup> This is offered as an explanation for the absence of any other abdominal lesion in this series. This is quite the opposite with staphylococcic infection, the presence of pyemic visceral processes being the rule. Ehringer,<sup>22</sup> in 1906, collected 21 cases of a similar type to that mentioned by the writer. Holt,<sup>23</sup> Martin,<sup>24</sup> Monks,<sup>25</sup> Bonnet,<sup>26</sup> Oppenheimer<sup>27</sup> and Dowd<sup>28</sup> have each recorded cases since Ehringer's report.

We believe that an acute inflammation of the nasopharynx, particularly of the tonsils, served as the original focus from which virulent organisms passed into the blood stream, reached the peritoneum and through their activity set up a violent peritonitis. We know that the peritoneum is, as a rule, unusually resistant to infection. What lowers the resistance of the peritoneum in these cases?

<sup>17</sup> Upsala Läkaref. Forh., 1900, vi, 248.

<sup>18</sup> München. med. Wehnschr., 1904, li, 1920.

<sup>19</sup> Boston Med. and Surg. Jour., 1905, clii, 346.

<sup>20</sup> AM. JOUR. MED. SC., 1912, cxliv, 502.

<sup>21</sup> Monographic Medicine, 1916, ii, 185.

<sup>22</sup> Arch. Pediat., 1906, xxiii, 268.

<sup>23</sup> Ann. Surg., 1906, xlv, 917.

<sup>24</sup> Lyon Méd., 1906, cvii, 821.

<sup>25</sup> Deutsch. Ztschr. f. Chir., 1906, lxxxiii, 456.

<sup>26</sup> Ann. Surg., 1908, xlviii, 821.

<sup>22</sup> Thèse de Paris, 1906.

<sup>28</sup> Ibid., 1908, xlvii, 964.

Shall we in accordance with the view that has been expressed by Rosenow claim that this particular type of streptococcus has a selective affinity for the peritoneum? Animal experimentation by Chapelle<sup>29</sup> in 1907 failed to establish any such selective affinity.

**RELATIONSHIP TO EPIDEMIC STREPTOCOCCIC SORE-THROAT.** Some dozen or more epidemics of septic throats are on record.<sup>30</sup> In those of recent years bacteriological studies have invariably proved a streptococcus as the offending organism. Capps<sup>31</sup> described it as a hemolytic capsulated streptococcus. Davis and Rosenow<sup>32</sup> found it to be a peculiar streptococcus. Later, Davis<sup>33</sup> acknowledged its close relationship to the *Streptococcus hemolyticus* and thought that the two were probably identical. This fact is of extreme importance, for although our cases did not occur during an epidemic of streptococcic sore-throat, yet the throats and peritoneal fluids yielded an identical coccus. We know that the *Streptococcus hemolyticus* sets up sporadic cases of tonsillitis and peritonitis. May not this organism, just as in the epidemics, infect the human body through milk and its products or by way of human carriers, be they handlers of infected dairy products, or those who have been in contact with cases of streptococcic angina?

Thorough clinical studies have, as a rule, not been made in these epidemics. Excluding Chapelle's investigations there is but scant mention of streptococcic peritonitis. The latter made a close study of the epidemic of septic throat which occurred in Helsingfors, Finland, in 1904. He reported eighteen cases of acute diffuse peritonitis, fourteen of which were beyond question secondary to angina of streptococcic origin. The most careful bacteriological studies were made. These proved beyond doubt that he was dealing with a streptococcus and not a pneumococcus infection. Mann<sup>34</sup> in his report does not mention the causes of the four deaths in the Concord, N. H., outbreak. Hamburger<sup>35</sup> records 9 cases of fatal peritonitis in the Baltimore epidemic. Invariably when looked for in these cases the streptococcus was found in the peritoneal fluid or venous blood at autopsy examination.

**ETIOLOGIC DATA.** Seven of the writer's eight cases occurred in females. Isolated cases occurring in males are recorded in the literature. Our cases were all in the young; their ages ranged from ten months to twenty-one years. All occurred during the winter and spring months. This corresponds exactly to the seasonal incidences of the streptococcic throat epidemics. Longcope and Fox<sup>36</sup> have

<sup>29</sup> Arb. a. d. Path. Inst. d. Univ. Helsingfors, 1907, Bd. ii, p. 583.

<sup>30</sup> Bull. Johns Hopkins Hosp., 1913, xxiv, 1.

<sup>31</sup> Jour. Am. Med. Assn., 1912, lviii, 1111. Capps: Jour. Am. Med. Assn., 1912, lxi, 723.

<sup>32</sup> Jour. Am. Med. Assn., 1912, lviii, 773.

<sup>33</sup> Ibid., 1912, lviii, 1852.

<sup>34</sup> Jour. Infect. Dis., 1913, xii, 481.

<sup>35</sup> Loc. cit.

<sup>36</sup> Bull. Ayer Clinical Lab., Pennsylvania Hosp., 1906, No. 3, i, 111.

found the *Streptococcus hemolyticus* occasionally in the throats of healthy individuals and have demonstrated that the virulent forms are more common in the mouths of healthy persons during the cold months. Throat cultures when done in our cases have yielded a streptococcus in pure culture.

**ANGINA.** In but few instances was there a history of pain in the throat or tonsillitis. By the time the patients were admitted to the hospital all evidence, except for an intensely hyperemic pharynx, were usually absent. In a few cases the gravity of the abdominal condition unfortunately caused one to pay but scant attention to the throat. Whether or not a previous exudate had been present is difficult to say. It is possible that in those cases there had been no reaction on the part of the tonsils and the streptococcus gained easy access to the blood stream. Marked enlargement of the cervical glands was absent in our series, evidence of nature's failure of defence against systemic invasion.

**PERITONITIC STAGE.** The history, as a rule, was that the patient had suddenly, while in the best of health, been taken sick with high fever, reaching 104° F., or over, severe generalized abdominal pain, repeated vomiting and marked prostration. These phenomena persisted until admission. When the peritonitis followed a distinct anginal attack we frequently found that a period of well-being, lasting three or four days, intervened before the sudden development of the peritonic symptoms. The temperature remained high without marked oscillations. The pulse was invariably very rapid and out of proportion to the temperature. It was at first of a bounding character. Herpes labialis was invariably absent in our series. Chapelle records its occurrence in a few instances.

Diarrhea occurred in but few of our cases. This is in contrast to the cases reported in the literature. Diarrhea is frequently stated to have preceded the peritonitis. This fact might argue for an intestinal origin in these instances. The leukocyte count was very high, ranging between 25,000 and 64,000, on the average 40,000. The polynuclear count varied from 85 to 97 per cent., on the average 92 per cent.

The abdomen was tender and moderately rigid all over. There was no marked distention, and careful examination only infrequently revealed evidences of fluid in the flanks. The patient rapidly passed into the terminal phase of peritonitis, with the usual attendant phenomena of Hippocratic facies, livid, clammy extremities and running, thready pulse. Death occurred in from three to eight days of the onset of the peritonic stage, and was the result of cardiac and vasomotor collapse, induced by a virulent toxemia.

Ehringer mentions three cases of subacute character which developed localized abscesses and recovered after incision and drainage. These were all of mild character, without prodromal signs, slight if any vomiting, and prompt subsidence of fever.

**BLOOD CULTURE.** Blood cultures were taken during life in but four of our cases. In only one was a positive culture obtained, which showed a streptococcus in pure culture. In this case a blood culture had been taken thirty-six hours after the onset of the illness. This corresponds to Libman's<sup>27</sup> findings of sterile cultures in his cases of acute terminating peritonitis occurring in chronic parenchymatous nephritis. Cultures would very likely yield positive results more often if they could be taken at the very inception of the peritonitic process and not on the second to fourth day after, as was unfortunately the case in our series. Chapelle in one instance recovered the streptococcus on the fifth day of the disease, which was one day after operation and two days before exitus. These instances of positive blood cultures during the course of the peritonitis are the only ones to be recorded in literature. A positive blood culture, especially very early in the course of the disease, speaks very forcibly for the hematogenous origin of the peritonitis, and cannot be ascribed to an agonal bacteremia.

**PROGNOSIS AND TREATMENT.** Because of the absence of any primary focus that can be surgically evacuated the prognosis must of necessity be bad. Ehringer's 3 cases of localized abscess formation recovered after operation and drainage. Five cases of Chapelle's group were operated upon and all died. In the Chicago epidemic, Capps and Miller<sup>28</sup> reported nine deaths from streptococcic peritonitis. They failed to mention if there were any cases that recovered. The inference is that all who developed this complication died. Early operation and drainage of the peritoneal cavity is indicated. This has resulted in the saving of 2 of our 8 cases, an unusually high percentage of recoveries. In these 2 cases the throat lesions and glands of the neck were markedly in evidence.

**OPERATIVE FINDINGS.** The peritoneal exudate varied from that of a thin serofibrinous to a fibrinopurulent character. Though Flexner, Manahan and Fishbein have, in the secondary peritonitides, shown that the character of the fluid is, as a rule, independent of the type of organism the peritoneal exudates of our cases were only exceptionally of the thick creamy character noticed in our primary pneumococcic cases. The peritoneal fluid yielded the *Streptococcus hemolyticus* in pure culture in seven cases and associated with the *Bacillus coli* in one case. This is highly instructive as compared with the fairly frequent finding of multiple organisms in the cases of peritonitis secondary to a lesion of an abdominal viscus. Mono-infection of the peritoneum would therefore strongly argue for a hematogenous source of infection.<sup>29</sup> As the *Bacillus coli* is seldom present in the blood infections it is highly probable that it was present as a secondary invader in the peritoneal exudate of our case.

<sup>27</sup> Bull. Johns Hopkins Hosp., 1906, xvii, 215.

<sup>28</sup> Loc. cit.

<sup>29</sup> Wilder: Tr. Chicago Path. Soc., 1916, x, 46.

Thorough search was made at operation for any gross visceral abdominal lesion. In no instance at operation or postmortem have we been able to find anything that could be accused of being the lesion responsible for the peritonitis; nor were there any evidences of cirrhosis, cardiac defect, chronic nephritis or other chronic disease present. These cases were therefore distinct from the terminating primary peritonitis of Flexner and closely allied if not identical with the streptococcic peritonitis found during epidemics of sore-throat.

**DIFFERENTIAL DIAGNOSIS.** Terminating primary peritonitis is superimposed on some chronic disease and occurs in either sex, while streptococcic peritonitis of the type herein described occurs in the previously healthy and almost exclusively in young females.

Pneumococcic peritonitis is in one-third of the cases secondary to pneumococcic lesions in the lung or pleura. The onset is stormy and the course of the disease is milder. The temperature is lower. Herpes is frequent. Subacute cases with localized peritonitis are more common, and these have a creamy, thick, peritoneal exudate. The prognosis is better. Throat cultures and peritoneal fluid show a pneumococcus on careful bacteriological examination. The streptococcic cases have a less sudden and milder onset, a prodromal period of angina, malaise and abdominal cramps. The course is very severe, nervous symptoms of toxemia are more marked and diarrhea may occur early and be persistent.

Pneumonia with pneumococcic appendicitis yields, besides the evidences of pneumonia, distinct localized rigidity and tenderness in the right lower abdomen.

Acute appendicitis, with subsequent general peritonitis, at the onset shows normal or only slightly elevated temperature. There is but slight vomiting. Diarrhea is rare. There is no marked prostration early; the pulse is then not very rapid and the rigidity for a considerable time is localized in the right iliac fossa.

Acute perforative peritonitis gives a history of a primary focus in a hollow viscus, *e. g.*, gastric or duodenal ulcer, gall-bladder disease, or intestinal lesion. The onset is marked by a very severe pain localized at the site of perforation. The temperature at the beginning is normal or subnormal. The abdomen during the first few hours is not rigid all over. The pulse-rate is not rapid until late. A secondary stage of apparent improvement occurs before the final general peritonitis supervenes. There is no diarrhea.

Acute gonococcic peritonitis gives previous symptoms and signs referable to the uterus or adnexa. Vaginal smears may yield gonococci. There is no marked abdominal rigidity. The symptoms usually abate in twenty-four hours. The great majority of cases recover. The temperature and pulse are lower. The peritoneal exudate is mostly in the pelvis and is usually of a dry fibrinous character, only occasionally purulent.

Typhoid peritonitis usually occurs late in the course of the disease. The enlarged spleen, positive Widal, typical roseola and blood culture assist in the differential diagnosis.

Localized tuberculous peritonitis is with difficulty to be distinguished from localized forms of streptococcic peritonitis.

Streptococcic sepsis is secondary to a suppurative focus in the body, is frequently complicated by acute endocarditis and blood cultures are repeatedly positive.

CASE I.—Sadie F., J. H. No. 25993, aged five years, was admitted into the service of Dr. William Linder on May 12, 1914. Two days ago she began to suffer with severe abdominal cramps, constipation, high fever and vomiting. These persisted on admission. She appeared splendidly nourished. Her cheeks were flushed. The abdomen was tender and showed a doughy rigidity all over. Temperature, 104° F., pulse, 160; respirations, 23. An enema resulted in the passage of sour smelling mucus accompanied by a few particles of feces. The urine showed a heavy trace of albumin, many hyaline and granular casts and a moderate number of red blood cells. Leukocytes, 28,000; polynuclears, 94 per cent. Operation performed the same day revealed thin, creamy pus in the peritoneal cavity, omentum congested and all abdominal viscera negative. Examination of the pus from the peritoneal cavity revealed the *Streptococcus hemolyticus* and *Bacillus coli*. The patient died five days later. No postmortem examination was permitted.

CASE II.—Annie G., J. H. No. 29330, aged ten months, was admitted December 18, 1914, into the service of Dr. William Linder. She had been sick for a few days with a high fever and marked prostration. Examination pointed to a general peritonitis. Preoperative diagnosis was pneumococcic peritonitis. Leukocytes, 60,000; polynuclears, 85 per cent. Temperature, 103.6° F.; pulse, 176; respirations, 60. Operation was performed immediately. On opening the peritoneal cavity there was an escape of a large quantity of seropurulent fluid containing flocculi. The appendix and other viscera were found normal. The child did not react and died during the night. Culture of the peritoneal fluid yielded the *Streptococcus hemolyticus*.

CASE III.—Gertrude K., J. H. No. 37041, aged twenty-one years, was admitted into the service of Dr. Ronsheim on April 8, 1916. Appendectomy had been performed seven years ago. Menstruation was, as a rule, irregular and at long intervals. She had given birth to one child. Last menstrual period thirty-three days before admission. On the day before her entrance to the hospital she was suddenly seized with severe cramps, high fever and vomiting. The symptoms persisted on admission. She was restless. Cervical glands were palpable. The abdomen was slightly distended, very rigid and tender throughout. Temperature, 104° F., pulse, 152; respirations, 28. Leukocytes, 20,000; polynuclears, 93 per cent.

Urine showed a faint trace of albumin and a few pus cells. Blood culture was sterile. On the mistaken diagnosis of a peritonitis, secondary to a tubal condition, a vaginal section was performed three days after admission. A large amount of thin pus escaped. This on culture yielded the *Streptococcus hemolyticus*. She died three days later. Thorough postmortem examination revealed no primary focus in the abdominal cavity.

CASE IV.—Lillian L., J. H. No. 31352, aged ten years, was admitted April 20, 1915, into the service of Dr. William Linder. One week before admission she was taken ill with a tonsillitis, which was treated for three days. After this period she felt well for two days. Two days before admission she was taken with a chill. Abdominal cramps, vomiting, constipation and high fever set in and persisted. Her face was flushed and cyanotic. The tonsils were large and together with the pharynx markedly congested. A few cervical glands were palpable. The abdomen was distended, slightly rigid and tender all over. Temperature, 105.8° F.; pulse, 160; respirations, 40. The urine was sterile on culture and yielded a trace of albumin. Leukocytes, 44,000; polynuclears, 96 per cent. A vaginal smear was negative for gonococci. Operation done on the same day failed to reveal any evident source for the marked general peritonitis present. A large amount of thin pus containing large green flocculi was evacuated. On culture this yielded the *Streptococcus hemolyticus*. The patient developed intra-abdominal collections of pus which caused a protracted temperature for one month. These collections were evacuated by means of the insertion of dressing forceps into the wound. The patient made a perfect recovery and was discharged cured just two months after admission.

CASE V.—Minnie E., J. H. No. 41321, aged six years, was admitted January 27, 1917, into the service of Dr. William Linder. Abdominal pain, fever and vomiting set in thirty-six hours ago. The vomiting was repeated three times. Bowels moved with enema. On admission the abdomen was seen to be distended, with generalized rigidity and tenderness. Temperature, 104° F.; pulse, 160; respirations, 40 and labored. The child was pale, drowsy and restless. Blood culture revealed the *Streptococcus hemolyticus*. Urine showed evidences of a marked toxic nephritis, heavy trace of albumin, many hyaline and granular casts and marked acetone. Leukocytes, 64,000; polynuclears, 92 per cent. Vaginal examination showed no gonococci. Operation was performed three and one-half hours after admission. The appendix and all other viscera except for superficial congestion were normal. A moderate amount of serofibrinous flakes were present in the pus. The peritoneal fluid on culture revealed the *Streptococcus hemolyticus*. The child did not do well and died on the fourth day after operation.

CASE VI.—Pauline E., J. H. No. 41424, aged nineteen years, was admitted into the service of Dr. William Linder, February 3,

1917. Three weeks ago she had suffered from general abdominal pains, which were intermittent in character. There were no gastric symptoms, no chills or fever. Her bowels were constipated. Three days ago she was suddenly seized with a dizzy spell, which was followed by persistent nausea and projectile vomiting. Paroxysmal generalized abdominal cramps were present. The temperature was high, ranging between 105° and 106° F. She had a persistent diarrhea, having five or six movements daily. There was no blood in the stool. On one occasion she vomited one-half tumblerful of clotted blood. This observation was made by her physician in attendance. These symptoms persisted to admission. Examination on admission to the hospital showed marked cyanosis and a state of collapse. The abdomen was tender all over. Shifting dullness was present. The extremities were cold and clammy. The patient was menstruating at the time. Blood culture taken the same day proved sterile. The urine showed a heavy trace of albumin and many hyaline and granular casts. Leukocytes, 40,000; polynuclears, 97 per cent. Temperature ranged between 102° and 104° F.; pulse, 120 to 160; respirations, 26. Herpes was absent. Lavage of stomach brought forth large amounts of foul light-brown fluid. The patient was moribund, and at the earnest request of the family that something be done, operation was performed the next day. On opening the peritoneum a large amount of non-odorous, sero-purulent fluid escaped. The appendix, tubes, ovaries, stomach, intestines and kidneys were investigated and found normal. Some pus was removed for examination and yielded a pure culture of *Streptococcus hemolyticus*. The next day the patient died. Complete postmortem examination was made the next day. Absolutely no trace of anything that might be interpreted as being the primary focus was found in the abdomen. Special attention was paid to the generative organs, which were found normal.

CASE VII.—Bessie A., J. H. No. 41958, aged twelve years, was admitted into the service of Dr. William Linder, March 10, 1917. She had an attack of diphtheria at three years, and since then has a persistent discharge from both ears. She suffered from repeated attacks of tonsillitis. Six days before admission she suffered from sore-throat, fever and dysphagia. She felt better the next morning. The next three days she was somewhat feverish, but was up and about and attended school. On the day before admission she was seized with generalized abdominal pain, which were most severe about the umbilicus. She was feverish, vomited and her bowels moved several times after an enema. On the day of admission these symptoms together with a moderate diarrhea were still present. Examination revealed a well-nourished girl with flushed facies. The pharynx was reddened. No exudate on the tonsils was present. Mucopus hung down the posterior pharyngeal wall. The abdomen was not distended and was markedly tender over the lower half. Rebound



tenderness (Blumberg's sign of peritoneal irritation) was present. The temperature was 104° F.; pulse, 140; respirations, 32. The urine was negative. Leukocytes numbered 23,000; polynuclears, 89 per cent. Culture of the ear discharge yielded the *Bacillus pyocyaneus* and a Gram-positive coccus. Operation performed the same day revealed a normal appendix. The intestines were covered over with flakes of exudate. A large quantity of seropus was present in the pelvis. Thorough investigation revealed no primary focus. The peritoneal fluid on examination showed a *Streptococcus hemolyticus*. Throat cultures yielded the *Streptococcus hemolyticus* and *Staphylococcus albus*. A catheterized specimen of urine before operation showed *Bacillus coli*. Blood culture before operation proved sterile. The temperature and pulse stayed up for the first six days after operation and then reached normal. The patient made an uneventful recovery. Rectal examination on discharge failed to reveal any pelvic exudate such as might result from a residual abscess.

CASE VIII.—Samuel E., J. H. No. 48864, was admitted April 7, 1918, into the service of Dr. J. B. Bogart. One week before admission the patient and his sister had partaken of some spoiled milk. They both vomited profusely. The girl was promptly relieved after rectal irrigations. The patient, however, developed a sore-throat and temperature of 103° F. The mother noticed that the child's abdomen became rigid. Generalized abdominal pain was complained of on the day of admission. Diarrhea was at no time present. On admission the child appeared very ill, with pinched facies, congested throat and marked generalized abdominal rigidity and tenderness. The urine was negative. The leukocytes numbered 28,800; polynuclears, 88 per cent. Temperature, 102° F.; pulse, 120; respirations, 30. Operation was performed the same day by Dr. G. I. Miller. The peritoneal cavity was filled with much seropurulent fluid. The appendix was kinked but not inflamed and was incidentally removed. Exploration revealed no primary focus. Two cigarette drains were inserted and the abdomen closed in the usual manner. The pus from the peritoneal cavity was carefully examined bacteriologically. An organism identical in its characteristics with the *Streptococcus hemolyticus* was recovered in pure culture. This organism showed no capsule, did not ferment inulin and did not dissolve bile. The temperature, pulse and respiration persisted high. Seven days after operation signs of pneumonia of the right upper lobe appeared. The child died four days later.

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## PATHOLOGY OF (MUSTARD?) GAS INHALATION.

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**INTRODUCTION.** The object of this paper is to offer a description of the gross and microscopic pathology produced by the inhalation of (mustard<sup>1</sup>) gas. Of the 37 cases included in this study, 35, according to the field medical cards, were due to mustard gas, 1 to mustard gas and phosgene and 1 to phosgene alone. In 34 cases the action of the gas on the respiratory tract was the main factor in causing death. Two died as a result of extensive skin burns, and 1 of cellulitis of the face and neck following burns in this region. It is evident that though the skin and eyes suffer from contact with this agent, and though death may result from injury in these areas, inhalation and the resulting pathology in the respiratory tract is the important factor in cases which reached this center.

The respiratory tract is attacked from the tip of the epiglottis to the terminal bronchioles and air vesicles. The effects seen here are due (1) to the intense irritation and escharotic action of the gas, and (2) to secondary infection, which promptly occurs. As seen in the autopsy room, more or less of the entire mucosa over this region is covered by a fibrinopurulent exudate, a false membrane, from dirty gray to yellowish or greenish-yellow in color depending somewhat on the amount of suppuration and blood pigments present. In many cases it covers the entire area from the tip of the epiglottis downward; in others it is in patches; and in relatively few does it cover the wall of the lower part of the pharynx.

The appearance of this membrane, both grossly and microscopically is very similar to that usually seen in diphtheria. In addition, the clinical features are not unlike those in the laryngeal type of this disease: hoarseness, temperature and frequently a relatively rapid pulse. Also, throat cultures often showed that many of them harbored the typical organisms. As a result, it not infrequently happened that perplexity arose in the differential diagnosis and several times an erroneous diagnosis of diphtheria, or *vice versa*, was made.

In nearly all cases the larynx is attacked. Here the false membrane extends down into all the irregularities of this region. The reaction is usually accompanied by more or less edema surrounding

<sup>1</sup> The term "mustard" gas is used because of the statements found on the clinical records, together with the character of the lesions which corresponds to that described in the literature.

the base of the epiglottis, the aryepiglottic folds and the false vocal cords. When the membrane is removed a deeply injected, hemorrhagic surface is revealed, usually showing shallow ulcerations. These are particularly likely to occur along the prominent and more rigid portions, such as the tip of the epiglottis and the edges of the vocal cords.

In the trachea and larger bronchi, much the same pathology exists. There is the same sort of membrane with the injection, hemorrhage and ulceration of the underlying tissues. Here also the ulceration tends to occur on the more prominent portions, such as the mucosa over the cartilaginous rings.

In cases of longer standing the membranous exudate is less in evidence and the ulceration of the tracheal and bronchial walls is more marked. In one case (Fig. 1) the mucosa of the lower half of the trachea and of the bronchi in the region of the bifurcation was of a greenish hue and literally riddled with ulcers, one of which was 1 cm. in diameter and extended through the cartilaginous ring to the outer fibrous coat of the trachea.

The lungs are usually very voluminous, due to a marked emphysema, largely vesicular, but occasionally interstitial or bullous. Subpleural hemorrhages are frequent. There may or may not be a pleurisy depending upon the extent of the secondary infection present. There is commonly the nodular feel of a bronchopneumonia and occasionally the solidity of a massive consolidation. The cut surface is characteristic. In very mild or very early cases there may be only congestion, hemorrhages and edema of the parenchyma surrounding the bronchial tree, together with emphysema of the peripheral portions; but ordinarily the exudate described as occurring in the trachea and bronchi extends down to the finest radicles, which are not simply lined with the membrane but actually plugged. These plugs project above the cut surfaces and may be squeezed out, much like comedones. About many of these bronchioles there is a larger or smaller area of infiltration, resembling bronchopneumonia, raised, grayish or dark red (if hemorrhagic) and dry and granular in appearance. The hemorrhagic areas are prominent. Outside the pneumonic area is the vesicular emphysema.

In the older and more advanced cases necrosis is frequently present in the consolidated areas, and this becomes the more prominent feature. This occurs particularly nearer the hilus where the pneumonic areas are larger, confluent and massive, but may also be seen in the centers of the smaller discrete areas. The necrosis gives rise to abscess cavities, the larger of which have ragged, irregular walls and are filled with thin, grayish, granular, purulent and necrotic material.

Microscopically the pathology is very interesting. In the upper respiratory tract the membranous exudate lining the lumen is exactly similar to that seen in diphtheria, consisting of masses of fibrin

mixed with occasional leukocytes, cellular debris and plasma. On the free surface of this exudate numerous clumps of bacteria are seen, principally diplococci. There is often no differentiation between the exudate and the mucosa of the trachea or bronchi. The epithelium is nearly everywhere absent. In a few places degenerating or necrotic cells can still be made out. The submucous tissue is infiltrated with leukocytes and is definitely edematous. There is not quite as extensive hyalinization of the fibrin, however, as one finds in a diphtherial membrane.

This type of exudate extends down into the bronchioles, where at times the lumina are completely plugged. The exudate is frequently seen attached at only one point, and here the membrane blends with the wall of the bronchiole so intimately that no differentiation is possible. The wall is markedly infiltrated with leukocytes, and this condition extends into the contiguous alveoli. In the unattached portions of the bronchial wall the epithelium may still persist. It is at the point of attachment of the fibrinopurulent membrane that the ulceration and necrosis apparently begins, and from there it extends into the deeper portions of the lung parenchyma, resulting in the formation of abscesses of the lung. In the upper portion of the tract, namely, the prominent edges of the epiglottis, vocal cords and cartilaginous rings, similar ulcerations are encountered. These ulcerations may perhaps be explained by the fact that the portions protruding into the lumen are attacked by larger quantities or by more concentrated mixtures of the poisonous gases. It is not impossible that minute droplets of the liquid gas itself are inhaled. In the lower portion of the tract the direction of the air current may determine the site of greatest injury.

The histological picture varies, depending upon the rapidity of death after the injury and consequently on the dose and concentration of the inspired gas. In several cases that came to autopsy the dose was evidently overwhelming, resulting in death from the escharotic and irritating action alone. In these rapid cases the prominent features are the edema, the profound injection of the bloodvessels and the hemorrhage. The edema generally differs from ordinary pulmonary edema in that the fluid escaping into the alveoli is considerably more albuminous, so that when coagulated it greatly resembles colloid. The fluid not only fills the vesicles around the bronchioles, but often is seen separating the cellular structure of the alveolar walls. In areas farther away from the bronchioles the albuminous fluid is deposited principally in the neighborhood of the alveolar walls, leaving clear spaces in the centers of the vesicles. Some areas show marked fibrin deposits lining the walls of the alveoli in a manner similar to the exudate seen in the bronchioles or even in the bronchi. The only difference noticeable is that there is a relative absence of leukocytic infiltration. In the centers of these alveoli there may be only a thin serum deposited

or a very fine fibrinous network; sometimes the space is entirely free from exudate. In older stages the fibrin becomes hyalinized and shows an infiltration of leukocytes and the presence of degenerating desquamated epithelial cells.

Such a picture as above described helps explain the very marked dyspnea and cyanosis so frequently encountered in these cases clinically. Both the albuminous fluid around the walls of the air vesicles and the lining by dense fibrinous masses must produce a very profound interference with the normal interchange of gases in the alveoli.

Another marked feature is the injection of the bloodvessels. In many of the bronchial walls the enormously dilated capillaries present a picture of a capillary hemangioma. Also the extensive hemorrhage, which is so commonly seen in the alveoli surrounding the bronchioles, gives a picture, with the low power of the microscope, which resembles a cavernous hemangioma of the liver. The capillaries of the alveolar walls are dilated and tortuous. It requires very little imagination to visualize the processes by which the extensive hemorrhages occur.

The histology of the peripheral portions of the lungs shows little except vesicular emphysema. In later stages, with advanced pneumonic involvement, pleurisy may be present.

In the older cases, that is, in cases which die of the secondary infection rather than from the direct effects of the gas, there is a picture of bronchopneumonia. But even here the marked edema and hemorrhage, along with the peculiar deposits of fibrin, make the diagnoses fairly easy. Areas of necrosis are now present. These apparently begin in the walls of the bronchioles and extend centripetally, forming occasionally large abscesses filled with pus and necrotic debris. Around these necrotic areas the alveolar walls often show thickening due to fibrosis and infiltration, with round cells and polymorphonuclears. The alveoli contain dense masses of precipitated serum or fibrin in various stages of organization. Some show only a slight infiltration with leukocytes; others show fibroblasts from the alveolar walls invading the masses; still others show fairly well-advanced organization of the exudate. These areas are generally small and surround the bronchioles in the regions where the abscesses are apparent. The picture is unlike the ordinary types of organization pneumonias, in that the areas of necrosis and the abscesses are more common. Some of the bronchioles also show organization of the exudate, so that if the case should go on to healing the bronchioles would probably become organized into fibrous cords.

No changes were evident in the bronchial walls that could be taken for bronchiectases. However, the various lesions seen in the bronchi and bronchioles might lead to great weakening and dilatation if the patient should go on to recovery.

Case Hosp. No.	after passing	Skin and eyes.	Larynx.	Trachea.	Bronchi.	Bronchioles.	Lung.	Clinical data.	Cause of death.
1 25-27	18	Extensive burns; severe conjunctivitis	False membrane; hemorrhage; ulceration	False membrane; hemorrhage; ulceration	False membrane; hemorrhage; ulceration	Plugged with thick exudate	Small patches of consolidation	.....	Skin, burns of, extensive.
2 25-32	6	Severe second degree burn of face, neck, buttocks, thighs; severe conjunctivitis	Heavy false membrane; surface ulcerated; edema of glottis	Heavy false membrane; lower part hemorrhagic	Thin fibrinopurulent membrane	Many completely plugged with thick purulent membrane	Edema; small patches of consolidation	Cyanosis; severe cough; pain in chest; albuminuria	Acute fibrinopurulent tracheobronchitis
3 25-38	6	Skin mild, not extensive burns; eyes inflamed	Purulent exudate; hemorrhagic	Injected; thin fibrinopurulent exudate	Thick fibrinopurulent exudate	Many completely plugged with thick exudate	Marked edema; moderate patches of consolidation	Fever; eyes swollen; pain in chest; delirium	Acute hemorrhagic and purulent tracheobronchitis.
4 25-39	6	Mild skin burns	Thick purulent exudate; hemorrhage; ulceration	Thick purulent exudate; hemorrhage; ulceration	Thick purulent exudate; hemorrhage; ulceration	Many completely plugged with thick exudate	Emphysematous; small nodules of consolidation	Fever; dyspnea	Acute ulcerative atrophic tracheobronchitis.
5 25-40	20	.....	Congested; thin layer of purulent exudate	.....	Congestion; fibrinopurulent exudate	Congested fibrinopurulent plugs	Small patches of bronchopneumonia; edema	Temperature; swelling of eyes; bronchitis and pulmonary edema	Acute suppurative laryngitis and bronchitis; bronchopneumonia.
6 25-45	29	Large superficial skin burns; eyes congested and lids ulcerated	Injected; thickened; yellow thick purulent exudate; ulceration	Injected mucosa thickened	Fibrinopurulent membrane	.....	Diffuse bilateral bronchopneumonia; edema; emphysema	Cyanosis; dyspnea; conjunctivitis; signs of bronchopneumonia	Acute suppurative tracheobronchitis and ulcerative laryngitis; bronchopneumonia.
7 25-48	17	Severe burns of genitalia; eyes acutely inflamed	Ulceration; hemorrhage	Thick fibrinopurulent membrane; hemorrhage; ulceration	Thick fibrinopurulent membrane; hemorrhage; ulceration	.....	Diffuse bronchopneumonia; emphysema marked	Fever; cyanosis and dyspnea	Acute suppurative and ulcerative tracheobronchitis; bronchopneumonia
8 25-50	12	Severe burns of face; severe conjunctivitis	Congestion; hemorrhage; thin yellow fibrinopurulent exudate	.....	.....	.....	Bronchopneumonia; diffuse; pulmonary necrosis; edema marked	Profuse expectoration; diffuse bronchitis; membrane on the soft palate	Bronchopneumonia and acute purulent tracheobronchitis
9 25-56	10	Severe conjunctivitis	.....	Thin yellow exudate; hemorrhage; ulceration	Thin yellow exudate; hemorrhage; ulceration	.....	Bronchopneumonia; diffuse emphysema and edema marked	Fever; cyanosis; dyspnea; diffuse bronchitis	Acute suppurative tracheobronchitis and bronchopneumonia.
10 26-16	3	Mild skin burns; severe hemorrhagic conjunctivitis	Hemorrhage; ulceration; purulent exudate; edema of glottis	Hemorrhage; ulceration; purulent exudate	Hemorrhage; fibrinopurulent exudate	Many completely plugged with thick exudate	Early bronchopneumonia; marked emphysema	Coma; dyspnea; cyanosis; temperature and rapid pulse	Acute hemorrhagic and suppurative tracheobronchitis and edema of glottis; bronchopneumonia.

11	20-18	4	Burn of genitalia; severe conjunctivitis	Hemorrhage; edema; plastic exudate	Hemorrhage; edema; plastic exudate	Many completely plugged with exudate	Early bronchopneumonia; marked emphysema	Cyanosis; dyspnea	Acute hemorrhagic tracheobronchitis; tracheopneumonia; Acute fibrinous bronchitis and edema of lungs. Severe skin burns.
12	20-26	13	.....	.....	Left has plastic exudate	.....	.....	Temperature; dyspnea; albumin and casts	
13	20-30	17	Severe second degree burns; severe conjunctivitis	.....	Congested; moderate purulent exudate	Congested	.....	Burns of skin only	
14	20-44	5	Severe conjunctivitis	Fibrinopurulent exudate	Congestion and fibrinopurulent exudate	Purulent exudate	Massive bronchopneumonia	Cyanosis; dyspnea	Bronchopneumonia; suppurative bronchitis and tracheitis
15	20-46	6	Congestion and hemorrhage in the conjunctive	Fibrinopurulent exudate	Fibrinopurulent exudate	Many plugged with heavy fibrinopurulent exudate	Moderate bronchopneumonia; edema	Dyspnea; conjunctivitis	Acute fibrinopurulent tracheobronchitis; bronchopneumonia
16	20-52	10	Second degree burns of scrotum; severe conjunctivitis	Hemorrhage; ulceration; fibrinopurulent exudate	Hemorrhage; ulceration; fibrinopurulent exudate	Purulent exudate	Bronchopneumonia	Fever; sore throat; signs of pneumonia	Acute suppurative ulcerative tracheobronchitis; bronchopneumonia
17	20-56	9	Slight skin burns; marked acute conjunctivitis	Thick exudate; vocal cords edematous and ulcerated	Heavy fibrinopurulent exudate	Plugged with thick exudate	Early bronchopneumonia	Dyspnea; cyanosis; fever; signs of pneumonia	Diphtheria; edema of glottis; acute suppurative and ulcerative tracheobronchitis; bronchopneumonia
18	20-59	25	Moderate skin burns; ulceration of eyelids	Plastic exudate; ulceration	Marked fibrinopurulent exudate	Many completely plugged with thick exudate	Marked bronchopneumonia	Fever; dyspnea; cough	Acute ulcerative and membranous tracheobronchitis; bronchopneumonia
19	20-62 A.	21	Moderate skin burns; ulceration of lids	Fibrinopurulent pseudomembrane	Hemorrhage; ulceration; fibrinopurulent exudate	Pus	Advanced bronchopneumonia; necrosis (early)	.....	Bronchopneumonia; ulcerative and membranous tracheobronchitis
20	20-74	17	.....	Fibrinopurulent pseudomembrane	Fibrinopurulent pseudomembrane	Many plugged with thick exudate	Early bronchopneumonia; edema; emphysema	Fever; hoarseness; cough; pain in chest; dyspnea	Acute suppurative tracheobronchitis; bronchopneumonia
21	20-1	11	Severe skin burns of face and neck; eyes burned	.....	.....	.....	.....	.....	Cellulitis of face and head following burns in these regions
22	40-32	7	Severe skin burns; eyes injected	Thick fibrinopurulent exudate; ulceration; hemorrhage	Thick plastic exudate; ulceration; hemorrhage	Many plugged with thick exudate	Edema	Dyspnea; pain in chest; weak pulse	Acute fibrinopurulent tracheobronchitis
23	40-34	4	Severe, not extensive burns; purulent conjunctivitis	Thick fibrinopurulent exudate; ulceration	Thick fibrinopurulent exudate; ulceration	Pus	Hemorrhage	Cough; dyspnea; cyanosis	Acute suppurative and ulcerative tracheobronchitis

Case No.	Days Hosp. after gas- ing.	Skin and eyes.	Larynx.	Trachea.	Bronchi.	Bronchioles.	Lung.	Clinical data.	Cause of death.
24	49-50	Slight burns of face; eyes swollen	Greenish-yellow fibrinopurulent exudate	Greenish-yellow fibrinopurulent exudate	Greenish-yellow fibrinopurulent exudate	Plugged with similar exudate	Bronchopneumonia moderate; edema	Fever; delirium; eyes swollen	Acute suppurative and ulcerative tracheobronchitis; bronchopneumonia.
25	49-51	.....	.....	Fibrinopurulent pseudomembrane	.....	Plugged with similar exudate	Bronchopneumonia; marked edema; emphysema	Fever	Acute fibrinopurulent tracheobronchitis and bronchopneumonia.
26	49-57	Mild burns of head, chest, arms; conjunctivitis	Fibrinopurulent exudate	Fibrinopurulent exudate	.....	Many plugged with similar exudate	Bronchopneumonia; marked emphysema	.....	Acute fibrinopurulent tracheobronchitis and bronchopneumonia.
27	50-2	.....	.....	Congested	Hemorrhagic	Hemorrhagic	Marked edema	.....	Acute hemorrhagic bronchitis; edema of lungs.
28	50-7	.....	Fibrinopurulent membrane; congestion; edema	Fibrinopurulent membrane; congestion; edema	Congestion; edema	Congestion; edema	Very marked edema	.....	Edema of glottis.
29	50-14	.....	.....	.....	.....	.....	Bronchopneumonia	.....	Bronchopneumonia.
30	50-19	Skin of face slightly burned; corneal opacity	Fibrinopurulent exudate; ulceration; hemorrhage	Fibrinopurulent exudate; ulceration; hemorrhage	.....	Many plugged with similar membrane	Emphysema	.....	Acute suppurative and ulcerative tracheobronchitis.
31	50-30	Few mild burns; conjunctivitis	Thin fibrinopurulent exudate and ulceration; edema of glottis	.....	.....	Many plugged with similar exudate	Early bronchopneumonia	Fever	Suppurative tracheobronchitis; bronchopneumonia.
32	50-44	Conjunctivitis	Pseudomembrane (gas and diphtheria); edema of glottis	Fibrinopurulent membrane	.....	.....	Hemorrhage	Fever; diphtheria	Septicemia; diphtheria; acute fibrinopurulent tracheobronchitis.
33	50-57	Conjunctivitis	.....	.....	.....	Pus	Massive bronchopneumonia	Violent cough, burning in chest; epiphora; nausea and vomiting	Acute fibrinopurulent tracheobronchitis; bronchopneumonia.
34	50-70	Acute conjunctivitis	.....	Numerous deep ulcerations	.....	Fibrinopurulent plugs and necrosis	Massive bronchopneumonia; abscess formation due to necrosis	.....	Gangrenous and ulcerative tracheobronchitis; lung abscess; bronchopneumonia.
35	19-1	Slight burns of face; congested conjunctivae	.....	.....	Injected	Pus	Bronchopneumonia; emphysema marked	.....	Bronchopneumonia.



In one of the cases studied the condition had gone on for several months and yet no bronchiectases were apparent in the lungs. In the cases of influenza-pneumonias studied in this center, bronchiectatic changes were relatively common and were apparent in lesions of much shorter duration. It is therefore quite likely that the lung pathology following influenza is more susceptible to the development of bronchiectasis than that following gas inhalation.

The pathogenesis of these lesions cannot be completely worked out from the material obtained at this center, because no cases came to autopsy under four or five days after exposure. However, by correlating the findings, and by making a composite picture of all the lesions encountered in the various stages of the disease, one might visualize the processes of reaction about as follows:

As the irritating gas is inspired, some of the exposed cells may become immediately necrosed. The capillaries nearest the surfaces become engorged. This is true also in the smallest bronchioles and perhaps in the alveoli themselves. The irritation causes an exudate consisting of a moderate quantity of heavy albuminous fluid in contradistinction to the huge quantities of thin fluid poured out in cases of phosgene inhalation. Later, cellular elements appear in the exudate along with desquamated epithelial cells. Some of the fibrinogen is converted into fibrin, which forms a lining not only along the upper tube of the respiratory tract but also may extend down into the terminal bronchioles and air cells. Depending upon the amount of irritation, the exudate, which is now fibrinopurulent in character, may increase in thickness until it may produce a layer 3 or 4 mm. in depth in the larynx, trachea and bronchi. There is at the same time a marked edema and congestion of the loose sub-epithelial cellular tissues. In proportion to the amount of congestion and the extent of the necrosis produced will be the extent of the ulceration along the larynx, trachea and bronchi and the hemorrhages in the lung parenchyma. The amount of exudate in the smaller bronchioles may become so abundant as to completely plug the lumina. This obstruction of some of the bronchioles will result in the compensatory emphysema of other portions of the lung.

The upper respiratory tract is constantly exposed to infection, which will soon result in a superimposed inflammatory reaction, due to the bacterial invasion. This infective process will gradually descend into the bronchioles, owing to the lowering in the resistance of the tissues. It is at this time that polymorphonuclear infiltration may become very abundant and produce miliary or submiliary nodules, which finally may become confluent. Because the gas is in the greatest concentration in the upper portion of the respiratory tract the greatest pathological changes will be produced around the hilus. If the necrosis is very extensive, very profound ulcerations may develop in the trachea and larynx, which may almost penetrate the walls. In the lung parenchyma the necrosis will gradually

develop into areas of hemorrhage and into abscess formation after the necrotic area becomes secondarily infected with bacteria.

If the patient receives severe burns in the respiratory tract but is still able to live for any length of time, for example, several months, then the resulting lesions will present the large areas of consolidation, pneumonic in character, through which will be scattered large or small areas of necrosis, with abscess formation. The attempt at healing will manifest itself by the definite evidences of organization of the exudate and the fibrosis, as previously described.

The following brief protocols are presented to illustrate the conditions found at autopsy in several cases of gas inhalation in which death occurred from five days to over two months after the injury. The first case is of a very early type while the last is an old and very advanced stage of the disease. Only the important data are given; the negative findings are omitted.

#### CASE REPORTS.

CASE I.—Autopsy 26-16. E. B. P., Sergeant, Co. H, 306 Infantry, No. 1702538. Aged twenty-two years, white. Died September 28, 1918, at 6 A.M., at Base Hospital 26. Autopsied September 28, 1918, at 10 A.M. Capt. Moses Barron, M.C., pathologist.

*"Clinical Data.* This case is that of a young man admitted to Base Hospital 26 at 6 P. M., September 27, 1918, from Hospital Train No. 63, with a diagnosis of gas, deleterious, absorption of, inhalation and surface contact. Temperature was 98°, pulse 156, respiration 20. The field medical card had been lost in transfer to the train. History obtained stated that he had been gassed three days previously. He was comatose, markedly cyanotic and breathed with great difficulty. The throat was reddened and swollen. The eyes were closed with purulent exudate. There were rales throughout the chest, with bronchial breathing suggesting consolidation. Diagnosis (addition) was made of bronchopneumonia, left lower lobe. September 28, temperature was 99°, pulse 108, respiration 16. Death occurred at 6 A.M.

*"External Appearances.* There is purulent exudate on the conjunctivæ of both eyes, with accumulation at the margins of the upper and lower lids. Small hemorrhages are present on the ocular conjunctivæ laterally to the corneæ. There is a vesicle around the external meatus of the urethra, 2 x 3 cm., and one on the anterior surface of the tibia, 1 cm. in diameter, 7 cm. below the patella. There is another vesicle, 2 cm. in diameter, 1 cm. below the internal malleolus, left.

*"Organs of the Mouth and Neck.* On opening the trachea and larynx there is found marked edema of the mucosa and submucosa. Pin-point hemorrhages, with minute ulcerations, are scattered over the entire epithelium. A purulent exudate covers the surface, very

marked over the vocal cords and at the base of the epiglottis. This is firmly adherent to the epithelium. The vocal cords are greatly thickened and the glottis appears almost completely closed through the approximation of the swollen tissues covered by the exudate.

"Lungs: On opening the bronchi they are found to be almost completely filled with tenacious masses of exudate. In the smaller bronchioles these assume a pseudomembranous character. They extend into the still smaller bronchioles as solid plugs, completely closing the lumina. On stripping the exudate the epithelium throughout shows pin-point hemorrhages, with minute ulcerations.

"Left: The lower lobe is large and voluminous. The lower half is feathery. It contains several irregular collapsed areas, reddish brown in color, in contrast to the grayish pink of the rest of the lung. There are firm, irregular masses present, which on section are reddish brown in color and contain grayish areas, 1 to 5 mm. in diameter, from the centers of which pus escapes from the bronchioles. The lower margin of the upper lobe is firm but crepitates slightly. On section, quantities of faintly turbid, blood-tinged fluid escape.

"Right: The right lung has only two lobes. The lower lobe is voluminous, light and feathery. The lower surface of the upper lobe shows numerous air vesicles varying from pin-point size to 2 mm. in diameter, situated along the interlobular septa. On section, quantities of pus escape from the large bronchioles.

"*Anatomical Diagnosis.* Edema of glottis; acute suppurative and ulcerative tracheobronchitis; beginning bronchopneumonia; edema of lungs; acute vesicular and interstitial emphysema; edema and congestion of the brain; congestion of the kidneys; gas burns of the conjunctivæ and skin.

"*Probable Cause of Death.* Acute suppurative tracheobronchitis, with beginning bronchopneumonia and edema of the glottis, following gas inhalation."

*Microscopic Study* (Section 46). The bronchioles are lined with a fibrinopurulent exudate. Some bronchioles are completely plugged. The plugs present a denser infiltration with leukocytes. The mucosa is nearly everywhere absent and the walls are infiltrated with polymorphonuclears. The capillaries are intensely injected. The alveolar walls immediately surrounding the bronchioles also show this injection of the capillaries, but the air vesicles contain relatively very little exudate. A few of the bronchioles are surrounded by a narrow zone of alveoli filled with polymorphonuclear leukocytes and some fibrin. There are small patches of edema in which the albuminous precipitate is very dense, resembling colloid.

Another section of the same lung shows an almost similar picture, but the purulent exudate in the alveoli is somewhat more marked.

CASE II.—Autopsy 25-32. W. B., Corporal, Co. F, 26 Infantry, No. 284685. Aged twenty-three years, white. Died October 14, 1918, at 2.45 A.M. Autopsied October 14, 1918, at 11 A.M. Capt. Moses Barron, M.C., pathologist.

*"Clinical Data.* This is the case of a man who was admitted to Base Hospital No. 25 on October 10, 1918, with extensive skin burns (second degree) over the face, neck, buttocks and thighs, due to mustard-gas contact. Inhalation of the same gas caused a severe inflammatory condition of the respiratory passages. Upon admission the patient was cyanotic, coughed frequently and complained of pains in the chest. Urinalysis showed albumin in the urine and hyalin and granular casts. The patient died at 2.45 A.M. on October 14, 1918.

*"Lungs:* The lungs and organs of the neck are removed *en masse*. The pyriform sinuses are covered by a thick, fibrinopurulent membrane, which is firm and adherent. The epiglottis is thickened and covered by a similar membrane. The entire larynx, including the vocal cords, presents a thick, shaggy membranous exudate, which, when removed, leaves a congested, necrotic and somewhat ulcerated surface. Portions of the exudate extend for a short distance into the trachea. Farther down into the trachea the mucosa is hemorrhagic, purplish red in color and covered by a thin hemorrhagic and purulent exudate, which becomes more marked in the bronchi and bronchioles where it almost occludes the lumina. On section of the lungs the cut surfaces are mottled, dark brown and red, with yellowish plugs completely filling some of the small bronchioles. On pressure large quantities of frothy fluid flow from the cut surfaces. The organs crepitate only slightly. Some of the bronchioles are surrounded by small grayish yellow, firm areas. The pleura is covered by a thin layer of fibrinopurulent exudate.

*"Anatomical Diagnosis.* Acute fibrinopurulent, hemorrhagic and ulcerative tracheobronchitis, with moderate edema of the glottis; early bronchopneumonia, with edema and congestion of the lungs; acute fibrinopurulent pleuritis; diffuse colloid thyroid; superficial burns of the skin from poisonous gas; mild acute diffuse nephritis.

*"Probable Cause of Death.* Acute fibrinopurulent and hemorrhagic tracheobronchitis, with edema of the lungs and partial edema of the glottis following inhalation of poisonous gas."

*Microscopic Study* (Section 426). The bloodvessels throughout the section are dilated and engorged. The bronchioles are plugged with fibrinopurulent exudate. In two bronchioles these plugs are seen to be attached to the wall at one side, at which point the mucosa is destroyed and the wall is edematous and extensively infiltrated with leukocytes. Remnants of mucous membrane are to be seen on the remainder of the bronchial wall. The capillaries in the wall are markedly engorged with blood. About the bronchioles there is extensive hemorrhage into the alveoli. Patches of hemorrhage alternating with emphysematous areas are scattered throughout the parenchyma. In some portions of the section the alveoli around the bronchioles are filled with a purulent exudate.

CASE III.—Autopsy 26-62. A. R. B., Private, Co. I, 61 Infantry, No. 2253041. Aged twenty-two years, white. Died October 31, 1918, at Base Hospital 26. Autopsied November 1, 1918. Lieut. Oliver C. Melson, M.C., pathologist.

*"Clinical Data.* This case is that of a man who was admitted to Base Hospital 26, October 12, 1918, with a gunshot wound of the right lumbar region. He was suffering from absorption of gas, deleterious, mustard, by inhalation and contact. (Clinical record is not available.) Death occurred October 31, 1918.

*"External Appearances.* . . . There are superficial ulcerations of the ears, eyes, nose and mouth. The skin of the right hand and forearm, both legs, both buttocks and back is pigmented. There are multiple superficial burns of the skin of the right arm, extending from 6 cm. above the elbow to 5 cm. below it on the lateral and flexor surface; on the flexor surface of the right forearm, 4 cm. in diameter; on the left forearm an area, 1 cm. in diameter, 2 cm. above the wrist-joint on the extensor surface, extending 2 cm. upward and inward; and also a smaller, more superficial burn, 5 mm. in diameter. The skin over practically the entire back is involved in superficial burns. . . . The posterior and inner surfaces of both legs, from the upper third of the thigh to 6 cm. below the knee-joint on the left, are involved in superficial burns as well as the anterior surface of the left knee-joint. There are also superficial burns over the external genitalia. There is a debrided wound, partially closed by silkworm sutures and drained by tubes, which extends from the midline (of the back) to the level of the third sacral segment and downward to the left trochanter. The mesial portion of the wound connects with the coccyx, which is fractured. . . ."

*"Organs of the Neck.* The mucous membrane of the trachea and larynx is covered by fibrinopurulent exudate, which is very adherent, appearing as a pseudomembrane. Near the bifurcation of the trachea the mucous membrane is hemorrhagic, with minute ulcerations scattered over the surface.

*"Right Lung:* The right lung is nodular and crepitant. The pleura is thickened and covered by many firm fibrous adhesions. The cut surface is dark red, moist and studded with irregular round raised areas, reddish in color. From the centers of these areas, yellow, purulent material can be expressed on pressure. Many are soft and necrotic, with a very foul odor.

*"Left Lung:* The left lung is nodular and crepitant. It is salmon colored and mottled with anthracotic pigment. The lower lobe is covered by shaggy, fibrous adhesions. At the apex of the upper lobe is a firm, grayish, non-aircontaining area, 5 cm. in diameter, which is granular to the feel and on pressure exudes large quantities of yellow purulent material. This area is sharply demarcated from the surrounding tissue. The remainder of the lung corresponds to the

right in description, except that the nodules are fewer in number. The bronchi contain a considerable quantity of frothy bloody fluid. The mucous membrane is markedly injected.

*Anatomical Diagnosis.* Advanced bilateral bronchopneumonia, with necrosis and abscess formation; acute hemorrhagic, suppurative and ulcerative tracheobronchitis (due to gas inhalation); multiple superficial skin burns; gunshot wound of the left buttock, with compound comminuted fracture of the coccyx; chronic adhesive pleuritis.

*"Probable Cause of Death.* Acute suppurative and ulcerative tracheobronchitis and bronchopneumonia."

CASE IV.—Autopsy 56-68. A. R. M., Private, Co. H., 312 Infantry, No. 3754421. Aged twenty-one years, white. Died January 3, 1919, at 3.45 P.M., at Base Hospital 56. Autopsied January 4, 1919, at 9.30 A.M. First Lieut. George W. Covey, M.C., pathologist.

*"Clinical Data.* This is the case of a man who was admitted to Base Hospital 26 on October 24, 1918, with the history of having been exposed to mustard gas on October 18. There were no skin burns, but the eyes were much inflamed. Examination showed the patient to be quite cyanotic, with marked conjunctivitis, accompanied by purulent discharge and ciliary injection. The pharynx was much injected; pulse good; heart negative; lungs showed many whistling rales throughout, with crackling rales in both bases most marked in the left posteriorly. No definite consolidation. Temperature 102°. October 27, smear negative for B. diphtheria. Dulness and suppression of breath sounds in areas in the right axilla and the right base posteriorly. November 25 he was much improved; still much semipurulent expectoration and cough; chest full of moist and sonorous rales. Heart rapid. Persistent afternoon temperature of 100°. November 30 the throat culture was positive for diphtheria and 10,000 units of diphtheria antitoxin given. He was transferred to Base Hospital 56 on December 1, with very marked membrane on both tonsils. Marked hoarseness. Given 30,000 units of diphtheria antitoxin at 3 P.M. December 3 was given 20,000 units of antitoxin at 9.10 P.M. December 4 the examination of the chest showed marked bronchial breathing all over the lungs, with many rales of all characters. Diagnosis: acute diffuse bronchopneumonia, bilateral, secondary to absorption of mustard gas; diphtheria, pharyngeal and tonsillar. He was given a total of 120,000 units of antitoxin. December 10 the patient had an attack of dyspnea lasting a few minutes. Examination showed respiration of asthmatic type, at the bases a few mucous rales, with areas of consolidation. There was a partial paralysis of the palate. December 17 his condition was about the same; sputum negative for tubercles. December 23 the patient had consolidation of right base of bronchopneumonic type. Quite dyspneic. January 3, 1919, his condition was worse;

unable to take nourishment; bubbling rales throughout lungs. Died at 4 P.M., January 3.

"Pleural Cavities: The left pleural cavity has a strong band of adhesions at the apex. There is no excess of fluid. The right also has a strong band of adhesions at the apex and no increase in fluid.

"Lungs and Organs of Neck: The organs of the neck and the lungs are removed *en masse*. The esophagus is normal. The tonsils, pharynx and upper portion of the larynx are normal. Just below the posterior extremity of each vocal cord there is an opening, about 5 mm. in diameter, leading into a cavity which extends into the laryngeal wall for a distance of about 1 cm. Pus can be expressed from these cavities; otherwise the larynx and upper 5 cm. of the trachea are normal. Beginning about 5 cm. below the larynx and continuing downward throughout the trachea and bronchi the mucosa is dark greenish in color, hemorrhagic and covered with pus. About 5 cm. above the bifurcation there is an ulcer with undermined edges, extending through the mucosa and through a cartilaginous ring to the outer coat of the trachea. It measures 1 cm. in diameter. From this point downward there are similar ulcerations becoming more and more numerous (Fig. 1).

"The left lung is voluminous, heavier than normal. There is a scar at the apex. Numerous hemorrhages are present beneath the pleura. There is marked vesicular emphysema. The cut surface of the upper lobe reveals a group of calcified nodules beneath the scar. The color is normal. Large quantities of pus are expressed from the bronchi and plugs of thick white exudate are expressed from the smaller bronchi and bronchioles. The cut surface of the lower lobe is dark red in color and practically every bronchus contains a plug of exudate which projects above the surface. Frothy bloody fluid exudes from the parenchyma.

"The right lung is heavy, large, firm, with marked vesicular emphysema and numerous hemorrhages beneath the pleura. The pleura is covered by a fibrinopurulent exudate. The cut surfaces of the upper and lower lobes are similar and as follows: Several large, ragged, irregular abscess cavities filled with thin grayish, granular pus, are scattered through the central portions of these lobes from the apex to the base (Fig. 2). They vary from a few millimeters to two or more centimeters in diameter. The central portion of both lobes is an airless, gray, granular mass—a central pneumonia. Toward the pleura the pneumonic areas become more discrete and are seen as gray, raised, granular areas varying from 3 or 4 mm. to 1 cm. or more in diameter, quite definitely circumscribed. In the center of each is a bronchiole from which a plug of exudate can be expressed. Occasionally the center of a larger discrete area is seen to be necrotic, with a small abscess cavity (Figs. 1 and 2). The parenchyma intervening between the pneumonic areas is dark red in color and emphysematous, with areas of

hemorrhage. Near the hilus are scattered areas showing interlacing, firm yellowish streaks suggesting organization.

*"Anatomical Diagnosis.* Marked gangrenous and ulcerative tracheobronchitis; marked fibrinopurulent bronchitis of smaller bronchi; massive bronchopneumonia, right, with extensive necrosis and abscess formation; healed pulmonary tuberculosis; right-sided fibrinopurulent pleuritis; chronic adhesive pleuritis; marked vesicular emphysema.



FIG. 1.—Larynx and trachea two months and ten days after gassing (Aut. 55-68, Case IV in text). Note extensive ulcerations, most marked at the bifurcation. The large transversely placed ulcer in the lower part of the trachea perforated through a cartilaginous ring.

*"Probable Cause of Death.* Gangrenous and ulcerative tracheobronchitis; bronchopneumonia, with abscess formation—following inhalation of poisonous gases."

*Microscopic Study* (Slide 449). The striking feature of the section is a small bronchus dilated and filled with pus cells. In the center of this mass is a group of vegetable cells and spirals. The wall of



the bronchus is only faintly visible, being infiltrated with polymorphonuclear leukocytes. The mucosa is entirely absent. The capillaries are intensely injected and dilated. In two places the wall is completely necrosed, and this necrosis extends for some distance into the parenchyma of the lung. About the bronchus and throughout the section there is thickening of the alveolar walls, which are infiltrated with polymorphonuclears and show a large increase of connective tissue. The alveoli are filled with fibrin and heavy

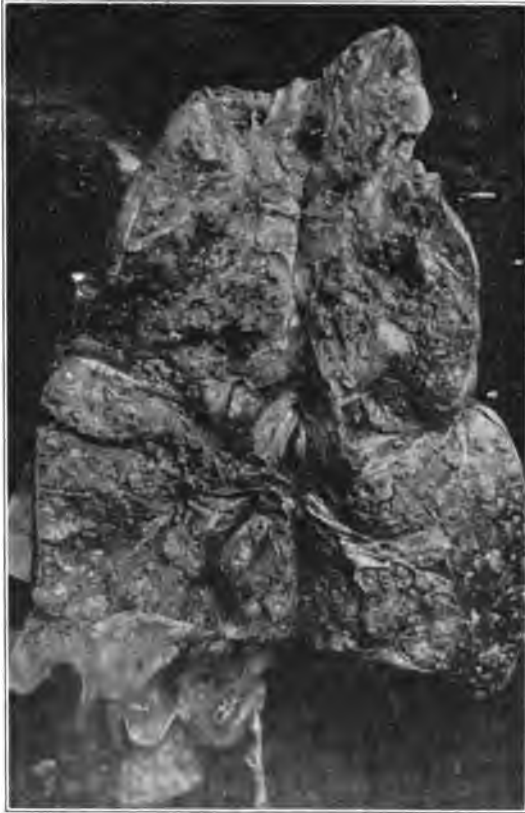


FIG. 2.—Lung from same case as Fig. 1. (The trachea and larynx are lying back of the lung, with the epiglottis and base of tongue showing just beneath the base of lung). Note the numerous areas of consolidation scattered throughout the cut surfaces. In the centers of many of these the emptied lumina of the bronchioles may be seen. Note the ragged areas of necrosis and abscess cavities.

precipitated serum through which are scattered a few cells. Fibroblasts are seen penetrating the exudate in numerous instances, and some alveoli are completely fibrosed.

DISCUSSION. Case I died the day after admission, and, allowing one day for transportation from the field, about five days after

gassing. Here are seen, as the outstanding features, edema, congestion, hemorrhages and very small ulcerations, with thin fibrino-purulent exudate in the upper respiratory tract. In the lower air passages one finds much the same picture with a more tenacious exudate which almost completely plugs many bronchioles. The parenchyma shows congestion, edema, emphysema, areas of atelectasis and very small bronchopneumonic areas.



FIG. 3.—Larynx and trachea from a case of mustard-gas inhalation. Note extensive edema of aryepiglottic folds especially the right; thick, shaggy membrane covering the larynx and vocal cords; membrane in patches on the wall of the trachea and bronchi; small ulceration of the wall near the bifurcation.

Case II died about six days after gassing. The exudate in this case is much more abundant than in Case I, and is shaggy and membranous. The ulcers in the trachea are a little more prominent. There is already a pleurisy present.

Case III died twenty days after gassing. The air passages show a marked pseudomembrane, and, upon its removal, a hemorrhagic and ulcerated surface. The lungs showed an advanced broncho-

pneumonia, with beginning necrosis and abscess formation in the center of some of the pneumonic areas.

Case IV died two months and ten days after being gassed. The air passages, trachea and bronchi show no membrane, but instead show marked necrosis of the mucosa, with large, deep ulcerations extending nearly through the tracheal wall. The lungs show extensive necrosis and abscess formation, accompanying a massive



FIG. 4.—Larynx and trachea from case of mustard-gas inhalation. Note thick membrane covering epiglottis, obscuring the vocal cords and extending in patches down the trachea; thick membrane on the walls of the primary bronchi; small ulcerations of tracheal wall near the bifurcation.

bronchopneumonia. The attempt at healing is shown by the organization of the exudate. Many alveolar walls are thickened and some alveoli are completely fibrosed. Strange to say, much albuminous deposit and fibrin are still in evidence in the air cells. Unfortunately, this case was complicated by clinical diphtheria, but most probably this complication did not materially change the lesions found at autopsy. Only one finding brings up a question of etiology: the evidences of the aspiration pneumonia as revealed by food particles lying imbedded in the purulent exudate within the small radicles of the bronchi. Was the aspiration of the material due to the par-

alysis following the diphtheria or to the deep ulcers in the trachea opposite the esophagus? The abscess formation might also have been augmented by the aspiration of the foreign material.

To recapitulate: Stage one, as represented by the first two cases, is characterized by mild edema, hemorrhage, beginning ulceration, early fibrinous deposit, emphysema and very early bronchopneumonia. Stage two (Case III) by a marked fibrinopurulent pseudomembrane, more extensive ulceration, emphysema, advanced bronchopneumonia and beginning necrosis. Stage three (Case IV) by ulceration, necrosis and abscess formation, with massive bronchopneumonia. The attempts at healing are revealed by the organization and fibrosis.

It is interesting to speculate on the outcome of a case similar to the fourth should such a case go on to recovery or if the lesions in the trachea should continue to progress. The tracheal ulcerations might easily perforate the wall, resulting in mediastinal abscess. Those in the bronchi near the bifurcation might ulcerate through and through and perforate the aorta. When such ulcers heal, contractures are sure to obtain. These contractures may result in traction diverticulæ of the esophagus. In the parenchyma, organization would occur and result in disseminated patches of fibrosis or even in extensive fibrosis of the lungs resembling healed tuberculous lesions. Some of the bronchioles might be transformed into fibrous cords through the organization of the exudate.

In milder involvement the walls only might go on to a fibrosis of a greater or lesser degree, which would result clinically in a chronic bronchitis. Upon the extent of the injury to the bronchial tree will depend the intensity of the clinical symptoms of convalescent and recovered cases, as manifested by the chronic bronchitis and emphysema. From what has been said above, many cases will undoubtedly present grave clinical difficulties in the differential diagnosis from pulmonary tuberculosis.

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### CLIMACTERIC HYPERTENSION: A STUDY OF HIGH BLOOD-PRESSURE DURING AND FOLLOWING THE MENOPAUSE.

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In this paper it is my purpose to describe a type of high blood-pressure developing in women at the time of the menopause and possibly the result of it, in which there is no discernible arteriosclerosis, at least, for some years after its onset, no renal involve-

ment and frequently no symptoms of any kind for possibly a decade or longer. In the early stages it is usually overlooked unless some intercurrent disease develops, and thus invites a thorough examination of an otherwise apparent healthy woman. Occasional references have been made in the literature on hypertension to a type occurring in women at the climacteric, but beyond noting the existence of such instances but little has been written.

Clifford Allbutt,<sup>1</sup> in 1903, against the then prevailing opinion that hypertension was always secondary to arteriosclerosis or nephritis, called attention to the fact that the hypertension in a certain proportion of cases was primary and the sclerosis secondary.

In 1914 Stengel,<sup>2</sup> writing on cardiorenal disease, noted cases of primary arterial or arteriolar disease, the onset and early course of which were so insidious that the history furnished little clue to the nature of the disease.

Arteriocapillary fibrosis as described by Gull and Sutton was at that time accepted as adequate to explain many cases of this type of cardiorenal disease, though in these days too much stress is laid upon renal disease as being the constant source of hypertension and of arteriosclerosis. Stengel referred to the frequency of hypertensive cases in which there was "considerable diffuse arterial thickening" (hard vessel walls, increased substernal dulness, ophthalmic findings), and the symptoms of which were almost wholly those of hypertensive cardiac involvement. He noted the occurrence of these cases in persons from forty to fifty years of age, and a greater frequency in women than in men. The patients were robust, with normal blood pictures and normal renal functional tests, the urinary examinations showing traces of albumin and hyaline casts. The high pressure and cardiac embarrassment were the most impressive facts. Thus on good grounds he separated these cases from primary renal disease.

Again, in 1915, Allbutt,<sup>3</sup> in a monograph, described a condition the essential feature and earliest manifestation of which was hyperpiesia or elevated blood-pressure. This has been termed "benign," "essential" or "primary" hypertension, and coincides with Janeway's "chronic hypertensive cardiovascular disease." Two years later Stengel,<sup>4</sup> in a paper on the "Classification of Chronic Nephritis and the Relation of Infection to Kidney Disease," further clarified the situation by a clear-cut classification of chronic nephritis in which he described "renal sclerosis" as falling into four possible forms, *i. e.*:

1. Primary sclerosis following acute interstitial nephritis.
2. Secondary sclerosis following glomerulonephritis or mixed forms of nephritis.

<sup>1</sup> Rise in Blood-pressure in Later Life, Med. Chir. Soc., 1903, lxxxvi.

<sup>2</sup> Cardiorenal Disease, Jour. Am. Med. Assn., October 24, 1914, lxiii, 1463-1467.

<sup>3</sup> Diseases of the Arteries, Including Angina Pectoris, 1915.

<sup>4</sup> The Classification of Chronic Nephritis and the Relation of Infection to Kidney Disease, Med. Clin. of North America, September, 1917, p. 217.

3. The terminal sclerotic kidney following arteriolar sclerosis.
4. The atrophic kidney of senile arteriosclerosis.

Stress was laid particularly on the third form, *i. e.*, the form following arteriolar sclerosis, in which the symptoms are not nephritic and the kidney condition and function remained unimpaired for long periods of time. As in his former paper, he noted the healthy appearance of these individuals and the frequency in which the patient was unaware of any illness. Marked changes in the retinal arterioles and sometimes retinal hemorrhages occurred in these cases. Of further interest he noted the rapid recovery of a man with elevated blood-pressure, albumin and casts, etc., after the cleaning up of pus pockets at the roots of the teeth.

Meara,<sup>5</sup> a year later, presented a series of his own cases, with a general discussion of essential hypertension. He also noted the occurrence of the disease in ruddy, stocky patients with *plethoric habits, active temperament, live men and women*. He describes them as gourmets if not gourmands, and emphasizes the influence of overeating as a causative factor.

The point which I wish particularly to emphasize from the study of my series of 51 cases of this type is the characteristic development of a type of hypertension in women, with its onset at the menopause or soon after, in which there is little if any evidence of fibrosis of the peripheral vessels, at least, for some years after the onset. The past medical histories in the cases I have selected are strikingly lacking in any of the predisposing or exciting causes of renal sclerosis or chronic nephritis, and this is in marked contrast to many of the cases presented by Meara, who includes a number of male patients. In both his male and female patients there are noticeably present some one or more infections in the past history or even of former attacks of nephritis. In his cases there was frequently a moderate retention of blood-urea nitrogen and at times some reduction in the phthalein. In short, the cases described by both Stengel and Meara would seem to fall well within the group of "renal sclerosis" and the subgroup renal sclerosis following arteriolar sclerosis, but undoubtedly include patients who could be placed in the group which I have selected from several hundred cases of hypertension, and which will now be described.

As mentioned above, the condition is, at times, discovered during the menopause, and at this time it has as its only indication a definite rise in both systolic and diastolic blood-pressure. The height of the pressure was in many of the cases very marked, running up to systolic 230-250-310 and diastolic 130-140-150. On the other hand, in the cases examined early in the course of the disease, pressures as low as systolic 180-190 and diastolic 100-110 were found. Rarely were lower figures noted, the higher ones being the rule.

<sup>5</sup> Hyperpiesia of Clifford Allbutt, *Med. Clin. of North America*, July, 1918, p. 1.

As it is at present these cases are frequently discovered in the course of a routine physical examination which has been prompted by some intercurrent disturbance or disease or at the time of a life insurance examination. Unfortunately, they are more frequently discovered several years after the menopause, when, following an indefinite period of vague symptoms, nervous, gastric or cardiac, the patient seeks relief and is surprised to know that her blood-pressure is high, and, by then, even very high. The majority of the cases fall within office rather than hospital practice, and possibly for this reason the literature on the subject is incomplete. Their appearance is strikingly healthy and their weight usually above the average; frequently they are obese. These women, usually from the upper social strata, are energetic, active and inclined to be of an intensely nervous temperament, used to good living and fond of life, but, nevertheless, subject to many worries and anxieties for years, as may be elicited in their histories.

The majority are discovered between the ages of fifty and sixty years, and it is toward sixty years, for the first time, that slight fibrosis of the peripheral vessels is noted, and during this period changes in the retinal arterioles make their appearance and thus occasionally an examination by the ophthalmologist may first reveal the condition.

Of the chief symptoms prompting the patient to consult medical advice, the gastric and nervous groups are the most common, the symptoms falling within the gastric neurosis group, with fermentation and constipation in marked evidence. Then nervousness and pains, chiefly in the limbs, were equally frequent. Headache and evidences of cardiac embarrassment come next in frequency, with finally a few cases complaining of weakness, vertigo, epistaxis, etc. However, headache was present in varying degrees in nearly all patients.

Contrasting this group of complaints with that of a group of renal sclerosis cases, with hypertension occurring in men between the ages of fifty and sixty years, I found that cardiac embarrassment and pain in the limbs had a decided preponderance over all other symptoms, and of equal importance in this differentiation is the fact that the peripheral vessels of the men patients were all markedly sclerosed in contrast to those of the women. Not only was there the difference of sclerosis in peripheral vessels, but also in the retinal arterioles which were involved, as a rule, in the male cases, regardless of age, while in the women the retinal sclerosis occurred in only two groups, the first group being those approaching sixty years or past and the second being represented by the occasional case in which there was a past history of scarlet fever, pneumonia, etc., or in which there was a local focus of infection as cryptic tonsils or diseased roots of teeth.

On the other hand the past medical histories of the men were rich

in the recognized causes of arteriosclerosis and nephritis, as rheumatism, pneumonia, scarlet fever, syphilis, typhoid, lead, alcohol and finally local foci of infection, almost all of which conditions were lacking in the histories of the women patients.

The blood picture again showed a distinct contrast, for of the male cases all but one were below the normal limit, while of the women it was the exception to find anemia, and when it did exist there was present some other disease which could readily account for it.

The contrast of the two groups is further noted in the urine analyses and the renal functional tests. In the renal sclerosis of male cases the urine contained a cloud or heavy trace of albumin and many hyaline and granular casts, the phthalein was considerably impaired and the blood-urea nitrogen slightly increased. On the other hand the cases in women showed, as a rule, but a faint trace of albumin, with hyaline casts in a few instances. The phthalein was impaired only when cardiac weakness had developed and the blood-urea nitrogen remained normal throughout. It was also normal even during periods of forced proteid feeding (Hopkins and Jonas<sup>6</sup>). There was quite a variation in the specific gravity of morning and evening samples in both groups.

I could cite other points of contrast in my endeavor to differentiate between these two types of hypertension, but I believe the above points are adequate to substantiate the differentiation, and to place, as a distinct entity, the hypertension of the menopause, which one might style endocrinal hypertension.

So far as I have been able to elicit from this survey of several hundred hypertension cases the true type of what has been called "benign" or "essential" hypertension, *i. e.*, hypertension without arterial or arteriolar sclerosis, is to be found only in women at or following the menopause. It may exist for a number of years without any distinguishable sclerosis, but in later years, *i. e.*, as a rule, from fifty-five to sixty years, sclerosis tends to develop and the ultimate termination is either a cerebral hemorrhage or a cardiac death. Throughout its course there is no evidence of kidney disease.

A brief presentation of a few typical cases may be of interest:

CASE I.—Miss M., aged fifty years, was admitted to the University Hospital owing to attacks of vomiting and weakness. She had never been ill before the onset of the above symptoms, which developed along with evidences of the menopause. She had been subject to many worries for years. Naturally of a nervous temperament, the nervousness had become aggravated with the onset of the attacks of nausea and vomiting. Palpitation was troublesome at times. She was chronically constipated. Physical examination revealed the following: Blood-pressure: systolic, 245; diastolic,

<sup>6</sup> Studies in Renal Function, with Special Reference to Non-protein Nitrogen and Sugar Concentration in the Blood, Phenolsulphonephthalein Elimination and Blood-pressure, Arch. of Int. Med., June, 1915, xv, 964-973.



125. Slight exophthalmos; thyroid enlarged. The heart was enlarged to the left and there was a slight systolic murmur at the mitral area, with accentuation of the aortic second sound. No peripheral sclerosis, and the eye-grounds were negative. The urine showed a specific gravity of 1017, there being neither albumin nor casts. Renal functional tests were also negative; phthalein elimination 70 per cent., and the blood-urea nitrogen 12 mg.

With rest and treatment the pressure fell to systolic, 170; diastolic, 90; and the patient became very much improved.

CASE II.—Miss P., aged forty-nine years, complained on admission of pains in the lower limbs. She had always been healthy aside from one attack of influenza and tonsillitis, and at twenty-nine years an exophthalmic goitre of several months' duration. Her menopause occurred nine years ago. She had been subject to hard work and many worries for years. Her present trouble she dates back two years, recurrent attacks of pain down the lower limbs being the chief complaint. Dyspnea on exertion and slight edema of ankles were noted on admission, and at times she was subject to headache.

Physical Examination: General appearance robust and obese (weight, 187 pounds). Blood-pressure: systolic, 195; diastolic, 120. Blood picture normal. Cardiac outline increased slightly to the left. Accentuation of aortic and pulmonic second sounds. No peripheral sclerosis, and the eye-grounds were normal. The urine showed a specific gravity of 1015, with neither albumin nor casts, and the phthalein elimination was 55 per cent.

Here again after treatment the pressure fell to systolic, 145; diastolic, 75, and there was marked improvement in the patient's condition.

These two hospital cases present interesting features in that their past histories were quite as negative as that of the average normal woman of their age. They had both been subject to nervous strain for years. In one the symptoms developed with the menopause and in the other not for several years later. In one the thyroid was enlarged and in the other there was the history of exophthalmic goitre in the past.

Peripheral and retinal arteriolar fibrosis were absent in both and renal function was normal.

CASE III.—Miss C. S., aged fifty-three years, first consulted me a year ago, complaining of stomach trouble. For four years prior to that she had been subject to intense nervousness, nausea, fermentation and constipation. She was also troubled with numbness and tingling in the limbs. All these symptoms developed with the onset of the menopause. She had been subject to worries for years. Her past medical history was negative aside from an attack of tonsillitis years ago.

Physical examination revealed the following: Well-nourished—

in fact, rather obese—woman, apparently in good health. Blood-pressure: systolic, 235; diastolic, 130. Blood picture normal, cardiac outline normal, systolic murmur at aortic and mitral areas with accentuation of aortic second sound. No evidence of fibrosis of peripheral or retinal vessels. The urine showed a specific gravity of 1025 and a trace of albumin but no casts.

CASE IV.—Miss A. M., aged fifty years, consulted me about two years ago, complaining of fatigue and nervousness, both of which she had noticed in varying degrees for four years, during which time and preceding it for three years she was troubled with hot flushes and menstrual irregularities. She was also subject to vague pains in the back. Her past medical history was negative.

Physical examination revealed a very robust, healthy looking woman. Blood-pressure: systolic, 250; diastolic, 140. Blood picture normal. No apparent increase in cardiac outline. Slight systolic whiff at the aortic and mitral areas, with accentuation of the aortic second sound. No evidence of peripheral or retinal arteriolar changes. The urine showed a specific gravity varying from 1011 to 1018, with a slight trace of albumin and no casts. Phthalein elimination, 82 per cent.

Under treatment her blood-pressure was readily controlled, though fatigue or excitement produced marked rises.

The last two cases are very typical of the office group, both occurring in patients of the better class and of the high-strung, intense, nervous type, and finally both being robust and without evidence of renal involvement or vascular changes.

Now in contrast it may be well to cite one of eleven cases kindly furnished me by Dr. Stengel, which would seem to illustrate the influence of gout on the vascular system, with possibly the superimposed influence of the absence of ovarian secretion and its consequent results.

CASE V.—Mrs. Y., aged sixty-one years, complained of pain and swelling of joints for the past five years. She was subject to headache, vertigo, palpitation, dyspnea and edema. Her past medical history was negative, aside from recurring attacks of gout and an operation for the removal of both ovaries, sixteen years ago, for a uterine tumor.

Physical examination revealed a well-nourished woman with very evident gouty changes in her joints. Blood-pressure: systolic, 310; diastolic, 160. Peripheral vessels markedly sclerosed and advanced arterial changes in the retina. The urine showed a specific gravity varying from 1007 to 1036, with a trace of albumin and an occasional hyaline cast. Phthalein elimination, 64 per cent. This case falls within the so-called hyperpiesia group or Janeway's cardiovascular group, but the advanced sclerosis and the past and present history of gout would readily exclude it from the group of menopausal hypertension cases above described.

The influence of castration in the occasional case in this series is interesting, but my data concerning it is, so far, too inadequate to permit of an expression of opinion.

Now, by way of contrast, I will go one step farther by citing two male cases, which by Allbutt and Meara would be classed under benign or essential hypertension, but which should be classified, I believe, in Stengel's group of renal sclerosis or the group of arteriolar fibrosis of Gull and Sutton.

CASE VI.—Mr. H., aged fifty-seven years, entered the University Hospital complaining of dyspnea and epigastric pain. These symptoms developed five months before, and gradually he noted vague pains in the limbs, palpitation, edema and constipation. His past medical history included scarlet fever, measles, gout, syphilis, Neisserian infection and the abuse of alcohol.

Physical examination revealed a well-nourished male of 170 pounds weight. Pus pockets at roots of the teeth. Blood-pressure: systolic, 175; diastolic, 130. Hemoglobin, 85 per cent. Cardiac area enlarged and heart sounds weak. Marked sclerotic changes in peripheral vessels. Wassermann reaction negative. The urine showed a specific gravity of 1010, with a trace of albumin and hyaline and granular casts. Blood-urea nitrogen 27 mg. and phthalein elimination 45 per cent.

Is there not sufficient cause for renal damage in this man's past history? The blood-urea nitrogen is only very moderately increased and the phthalein moderately reduced, but in spite of quite fair renal function it would seem inevitable that the fibrosis should have involved the renal vessels to a fairly marked degree.

To select another illustration from the group of male cases:

CASE VII.—Mr. G., aged fifty-four years, was admitted to the University Hospital in an unconscious condition. Prior to this sudden attack of unconsciousness he had noticed some weakness and occasional blurring of vision, but no other symptoms. His past medical history included repeated attacks of acute rheumatic fever and the abuse of alcohol, besides having done heavy physical work for years.

Physical examination revealed a male of medium build. Blood-pressure: systolic, 195; diastolic, 110. Hemoglobin, 70 per cent. Pus pockets at roots of several teeth. Cardiac area enlarged and muscle tone poor. Peripheral and retinal arteriolar sclerosis advanced. The urine showed a specific gravity of 1013, with a cloud of albumin and many hyaline and granular casts. Blood-urea nitrogen 20 mg. and phthalein elimination 50 per cent. Here, as in the above case (No. VI), we have marked fibrosis of the vessels, albumin and casts in abundance, yet fair renal functional tests. But here also, as above, the past medical history contains sufficient evidence to account for the general sclerotic changes and probably renal changes as well. Besides the histories, both patients had

faulty dental conditions, which could in themselves furnish a local source of intoxication and contribute to the condition.

These cases, I think, illustrate clearly the contrast between arteriolar disease, with probable renal sclerotic changes on the one hand, and on the other the menopausal hypertension group, which seems to be in a class alone, and which, to me, represents the only true type of "benign" hypertension.

How correct the term "benign" is I question when I look back over the records of these patients for several years. They usually do well under treatment, but their desire to overdo and their naturally nervous temperament are their worst enemies.

**ETIOLOGY.** The etiology of this condition will bear investigation. I have shown above that these cases are usually free from the causative factors of arteriosclerosis and nephritis as accepted today. Overeating, as suggested by Allbutt, may be and probably is a contributing cause of "hyperpiesia," accepting that term in the sense in which he used it. I cannot see that it has been a contributing cause in this series of menopausal hypertensive cases.

Mental strain and worry and a naturally nervous temperament when superimposed on the profound emotional and bodily changes occurring at the time of the menopause would seem to be more naturally provocative of the trouble. Marriage and child-bearing seem to play no part, as many of the cases were single, and of the married, some had children and others had not.

To consider then the influence of the menopause on the production of this type of hypertension, certain established facts must be presented in support of this theory.

"The ductless glands by their correlation form a perfect physiological balance which is preserved by a proper distribution of harmony and antagonism between the functions of the various glands.

"If one of the glands is diseased or extirpated the normal balance is upset and the organism of the individual may be affected by the abnormal action of one or more distant glands of the group."

In considering the glands of internal secretion, I wish particularly to call attention to the adrenals, pituitary body, thyroid and ovaries.

The medulla of the suprarenal system elaborates the hormone adrenalin which influences the sympathetic nervous system, blood-pressure, the distribution of blood and the tonus of organs innervated by the sympathetic system. This hormone of the chromaffin system is in turn greatly influenced by conditions of emotional disturbance and certainly during the menopause, in some cases, the emotional disturbances are profound. The relation of the suprarenal system to the glands of sex is illustrated by the cortex, lipoid granules being present in it, just as they are in the interstitial and luteal cells of the ovary. Furthermore, the cortex enlarges during breeding and pregnancy (Vincent<sup>7</sup>).

<sup>7</sup> The Experimental and Clinical Evidence as to the Influence Exerted by the Adrenal Bodies upon the Genital System, Surg., Gynec. and Obst., September, 1917, xxv, 294.

Functional activity of the hypophysis is closely related to that of the sex glands, extracts of the anterior lobe having a distinct influence on the sexual apparatus, and the gland enlarging during pregnancy. Of further interest bearing on this subject of hypertension, extracts of the posterior lobe when administered clinically produce an elevation in blood-pressure.

"The ovary is recognized as a true organ of internal secretion. The corpus luteum in its full development presents the characteristic picture of an internal secretory gland. It develops at the age of puberty, and coincident with this is the appearance of the cyclical changes of menstruation, which changes disappear after the cessation of the corpus luteum formation at the climacteric. The atretic follicles are believed to be the further source of internal secretion of the ovary, the absence of the corpus luteum being sufficient evidence that there is some other portion of the ovary used for the primary source of the secretion. There is much to show that the action of the ovarian secretion is neither direct nor selective, but that it exerts only a balancing influence on other correlated and more powerful glands, the activity of which the ovarian secretion discharges or suppresses as the case may be. With the hypofunction of this gland we have not only to consider the effects of diminished secretory power, but also the changes wrought in the other members of the group, the balance of whose function has thus been disturbed.

Furthermore, the influence of castration after maturity has led to variations in sugar assimilation, coagulation time of the blood and chemical composition of the blood, as well as a tendency to adiposity.

"Variations in the size of the thyroid gland during certain phases of the female sexual life have been recognized for years. Marked enlargement at puberty, with associated palpitation and evidences of vasomotor disturbances, are attributed to a hypersecretion of the gland at this period. Early extirpation of the thyroid not only produces degenerative changes in the ovaries, but delays the time of puberty and limits the productivity of the individual, and, further, women with diseased thyroids usually have menstrual disorders.

"An interesting observation of Lange is that women in whom the thyroid does not swell exhibit a renal albuminuria, and he expresses the belief that the swelling of the thyroid acts as a protection against certain poisons which are set free as a result of pregnancy, and which, without the protection of the secretion from the hypertrophied thyroid, are injurious to the kidneys" (Graves<sup>8</sup>).

Several instances of exophthalmic goitre have occurred at the climacteric and have led to the suggestion that the neuropathic and vasomotor symptoms of the change of life are the result of hyperactivity of the thyroid gland.

Illustrative of the effect on the endocrine glands of emotional

<sup>8</sup> Gynecology, 1918.

stress are the results of Etinne and Richard,<sup>9</sup> who observed several patients who had been in Nancy during repeated violent bombardment from big guns and aëroplanes. They cite the development of exophthalmic goitre in an acute form, with high blood-pressure in two women of twenty-four and thirty-four years. They also noted that in some women menstruation was arrested by the bombardments. In one man Addison's disease appeared and was followed by the symptoms of exophthalmic goitre, and in two other instances Addison's disease became superimposed on preëxisting exophthalmic goitre.

These cases are especially interesting in that they show exophthalmic goitre of emotional origin may develop with suprarenal hyperfunctioning as well as with hypofunctioning, and, further, that the suprarenal trouble may also become superimposed on exophthalmic goitre.

The correlation of these glands I have dealt with at some length, noting the more important recent clinical and experimental evidence, with the intention of presenting, as the possible cause of menopausal hypertension, a disturbance in their functioning. As mentioned above the disease is lacking in any other clear-cut etiological factor.

At the menopause, with the withdrawal of at least a part of the internal secretion of the ovary from its place in the connecting link of endocrine glands, it would be a natural assumption to consider that a certain amount of depressor influence of the ovary was withdrawn from the adrenals, hypophysis and thyroid, leaving them, as it were, out of balance.

Knowing that there are produced in one or more of these glands substances that increase blood-pressure, influence the sympathetic nervous system (vasomotor system) and the sex glands, aid in regulating metabolism, and, finally, exhibit an intimate relationship with emotional disturbances, it does not seem improbable that the blood-pressure is, by a combination of these altered influences, raised and sustained at a high level. A persistently high pressure of this type will, in the course of years, produce fibrosis of the vessels, and this we have seen develop in the latter years of these patients, though I have known them in a few instances to reach sixty years and over without the slightest evidence of peripheral or retinal sclerosis. If a routine blood-pressure were taken of all women at the menopause I believe the results would be of great diagnostic and therapeutic benefit for the patients' future.

NOTE.—Prognosis and Treatment will be given in a later paper.

<sup>9</sup> Exophthalmic Goitre and the Bombardments, *Bull. de la Soc. méd. des Hôp., Paris*, December 20, 1918, No. 36, xlii, 1196.

## REVIEWS

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**SURGERY OF THE SPINE AND SPINAL CORD.** By CHARLES H. FRAZIER, M.D., Professor of Clinical Surgery in the University of Pennsylvania. Pp. 909; 378 illustrations in the text. New York and London: D. Appleton and Company.

THE appearance of this large volume limited to the field of the spine and spinal cord by a master of the subject is an event of importance to the great army of surgeons who cannot hope to attain special experience and knowledge in this branch of surgery. To the ordinary surgeon who cannot keep abreast of the literature of this and other fields of general surgery, the only available guidance comes from text-books and systems of surgery. It was the author's purpose to discuss the conditions so comprehensively that it would not be necessary for the reader to consult collateral works. To this end special authorities have contributed chapters on anatomy, normal and pathological physiology, cerebrospinal fluid and its relations to spinal diseases and on the roentgen-ray examination. Pierson devotes 96 pages to a detailed discussion of the anatomy, including its histological and embryological aspects, and lays a strong foundation which is very important. Allen covered the normal and pathological physiology thoroughly and interestingly. The part played by the cerebrospinal fluid in spinal surgery, as brought out by Kolmer will be of great value to most surgeons because such information is usually not readily available to them. Pancoast's presentation of the roentgen-ray examination of the spine is replete with excellent roentgen-ray illustrations and valuable points drawn from his long and rich experience.

The purely clinical aspects of the whole field are discussed by Frazier in the remaining portion of the book, about 650 pages. He devotes special chapters to spina bifida, trauma (chiefly sprains, dislocations and fractures, and their complications), stab and gunshot wounds, tumors and meningitis. Other chapters are given to surgery of the spinal roots, rhizotomy, lumbar puncture, intraspinal therapy, spinal anesthesia, laminectomy, chordotomy and decompressive laminectomy.

The special appeal of the volume to most surgeons will come from the author's rich experience and intimate knowledge on subjects the average surgeon knows little about because he rarely meets

with them and because the sum total of available information is not particularly great. He may now have at his easy disposal a well digested resumé of the most advanced thought on each of the subjects discussed, with a wealth of excellent illustrations. It is something he has long felt the need of and he will surely take advantage of the opportunity now afforded to have this volume within easy reach when the need again arises.

T. T. T.

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DISEASES OF THE HEART AND BLOODVESSELS. By THOMAS E. SATTERTHWAITE, A.B., M.D., LL.D., Sc.D. Pp. 328; 42 illustrations. New York: Lemcke & Buechner.

THIS work, with a chapter by Dr. W. Wayne Babcock, of Philadelphia, on cardiac surgery represents to a great extent, a compilation, with revision, of the various publications of the author. In general the chapter arrangement meets with our approval, but we, although acknowledging the thoroughness of Satterthwaite's methods, scarcely recognize as so important in a book of this kind the chapter on cardiac parasites and Graves's disease. There are many good points in the book which overbalance some features to which the reviewer may take exception. The author in one place makes the observation that diastolic pressure readings will be inaccurate "if the examiner's hearing is defective" and if the patient's general circulation is poor, and on this account he remarks that life insurance examiners are not expected to give special weight to diastolic readings. In another place he emphasizes how easy diastolic pressures may be read and how important the estimations are. Deafness in a physician can scarcely be a sufficient cause for discouraging the taking of diastolic pressure. Satterthwaite believes diabetes and Graves's disease are associated with hypotension, with which statement the reviewer takes issue. Also, we find that all intestinal toxemias have hypotension (p. 68); yet, on page 70, when he skims over the management of hypertension he recommends certain things to combat intestinal toxemia in order to reduce hypertension.

He says endocardial murmurs are of two kinds, organic and functional, the former heard "when there is a mechanical hindrance to the flow of the blood from ulcerations, etc., of the valve." What of the regurgitant murmurs? We do not like this sentence. "The right ventricle gets to be hypertrophied" (p. 98). We find no mention of the Graham Steell murmur in Mitral Stenosis, although we believe this valve lesion is otherwise well described. On page 116 an American author is given the credit for emphasizing the difference between arm and leg pressure in aortic disease, but if



reference is to be made to this important phenomenon, why not refer to Leonard Hill? Also, we find no mention of increase of pulse-pressure in aortic insufficiency, although pulse-pressures (p. 18) are said to be very important. On page 152, the revival of a man by the pulmotor four hours after his heart had ceased to beat, is quoted, but why and wherefore? Strange things have occurred in medicine, but not that!

The reviewer having had charge of cardiovascular examinations in the Army was charmed by this paragraph: "In the examination of recruits it is important that the man examined should not be allowed to remain long standing prior to his examination. The quarters should also be warm and agreeable and the examiner cheerful and not abrupt in his methods." "'Tis a consummation devoutly to be wished," but, we fear, in this cardiovascular boards failed signally and never attained the beautiful ideality described by Satterthwaite.

There are more minor and major points in the book which may be criticized, among them incorrect spelling of proper names; but it is time to praise. Apart from the undoubted impression which the reviewer received from the book, to wit, that it was prepared hastily, there is much of value therein. The description of electro-cardiograms and other polygrams is good, also arrhythmia, and the illustrations, mainly by the author, are good, although there is a mistake in numbering, which is confusing. On page 180 there is Fig. 41 and on page 246 Fig. 86, but what has become of the intermediate figures? We could find none.

Although commendable, we must repeat, the book seems to us to have escaped the drudgery of revision and to have suffered from having escaped. The chapter by Dr. Babcock on surgery of the heart is a good and concise compilation, but it may be questioned whether such a chapter, however valuable in a comprehensive treatise, has a place in a volume from which much of importance has been omitted in order to reduce the size of the book.

E. H. G.

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PHYSICAL AND OCCUPATIONAL REÉDUCATION OF THE MAIMED. By JEAN CAMUS. Pp. 195; 64 illustrations. New York: William Wood & Co., 1919.

THIS book has left the reviewer with the impression that too much has been crowded into a few pages, hence the feeling that only the surface has been scratched. One point has been emphasized, and that is the futility of all reconstruction work unless the disabled man puts his heart into his treatment. Not only physical reconstruction is needed, but psychic reconstruction as well. Having

been in several general hospitals where such work is being carried on, the reviewer has been, indeed, impressed with the difficulties surrounding the reconstruction of a man who does not desire to be reconstructed and the insidious permeation of this man's attitude among those who are eager to be benefited. Illustrations add much to the text of Camus's book, which has been ably translated by W. F. Castle. Articles on British institutions have been contributed by British authorities, including Sir Arthur Pearson. Mechanical appliances are described, and the several occupations a maimed man can be trained to fill are well discussed. E. H. G.

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QUARTERLY MEDICAL CLINICS. By FRANK SMITHIES, M.D., at Augustana Hospital, Chicago. Vol. I, No. 1 Pp. 188; 42 illustrations. St. Louis, Mo.: Medicine and Surgery Publishing Company, 1919.

WHAT may be termed the "Chicago Idea" of publishing for general information the work of the clinics of that city is augmented by this volume from the prolific pen of Dr. Smithies. The reviewer has found the *Quarterly Medical Clinics*, which is described as "A Series of Consecutive Clinical Demonstrations and Lectures," a very successful record of the clinics and lectures given to the senior students of the University of Illinois.

We have no doubt of the future success of Smithies's undertaking if this first volume is a sample of the works which will follow quarterly. The subjects have been well selected, the exposition of the cases has been carefully written and the deductions on which the ultimate diagnosis and treatment have been based are logical and consecutive. Not only senior students but medical practitioners as well should find much of value in this new volume from Chicago. E. H. G.

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THE HUMANE SOCIETY OF THE COMMONWEALTH OF MASSACHUSETTS: AN HISTORICAL REVIEW, 1785-1916. By M. H. DE WOLFE HOWE. Pp. 398. Illustrated. Boston: Riverside Press.

It is a pleasure, and may we say a relief, to turn from purely medical literature to the perusal of a book which makes its appeal to the general public rather than to the medical profession, for in this book we are told interesting things of how the Humane Society was formed to prevent the bugbear of those days, premature burial; of ancient methods of reviving those apparently dead; of the rewards given to the person who shall first discover and endeavor to recover the subject; of the development of life-saving at sea; of the

founding of the Massachusetts General Hospital! What a controversy took place over placing a drowned child in bed between two persons of good constitution, as the "salutary effects of the natural vital warmth have been clearly proved in a variety of successful cases!" What a discussion about the value of blowing tobacco smoke into the bowel! And we may imagine the storm aroused by the recommendation not to bleed those supposedly dead!

Engravings, profuse and beautiful, illustrate the text. Original documents are reprinted, original odes and poems, noteworthy for their purport, not for their poetic value, quaint in their thought, ponderous in their expression, all add to the enjoyment of Howe's splendid production. From the standpoint of the historian the work is invaluable; as a picture of the noble activities of a group of early humanitarians it is irreproachable; that it is an interesting book is undeniable.

E. H. G.

#### GILBERTUS ANGLICUS MEDICINE OF THE THIRTEENTH CENTURY.

By HENRY E. HANDERSON; A.M., M.D. Pp. 77. Cleveland, Ohio: Published posthumously for Private Distribution by the Cleveland Medical Library Association.

THIS book by the late Dr. Handerson, is of interest to the antiquarian as a picture of medieval medicine, containing as it does a fascinating description of intestinal surgery, with an account of the use of drainage tubes of alder. The work reflects much credit upon the author's industry in a research, which now the public is permitted to enjoy.

E. H. G.

WAR SURGERY FROM FIRING LINE TO BASE. By BASIL HUGHES, Temporary Major, R.A.M.C., T.F., and H. STANLEY BANKS, Captain, R.A.M.C., T.C. with special chapters by Lieut.-Colonel L. F. Smith, R.A.M.C., and Miss C. Bilton, R.R.C., Q.A.I.M.N.S., and an introduction by Col. Sir T. CRISP ENGLISH, Consulting Surgeon to the British Forces in Italy. Pp. 623; 373 illustrations. New York: William Wood & Company, 1919.

Of the many books that have recently appeared on military medicine and allied topics, this volume seems to take the honors, because of the interesting manner in which the subject is presented. Although by title it is a treatise on war surgery, in fact it represents the personal experiences of two British medical officers who had spent three and one-half years both in the Western and Eastern theaters of war. During this time they were attached to regiments on the firing line for eighteen months, with a field hospital eight

months; they were with a busy casualty clearing station in France for four months and spent a year at a base hospital in the East. All of their statements are based upon personal observation, and most of the subjects are illustrated by actual case histories. The reader's interest is held throughout by the entertaining narrative style, including the use of many words of trench slang, which gives a wonderful insight into the life and hardships of the soldier as well as the surgery of the war.

Bacteriology and wound infections, as may be expected, have been extensively considered; in fact, many of the details of laboratory technic could have been omitted without detriment to the general value of the book. The chapters on war wounds are fascinatingly gruesome, and it is of interest to note that the Carrel-Dakin technic, when properly and systematically applied, has been found to be far superior to the other treatments. In addition to the discussion of the purely surgical aspect of the soldier, the book contains many valuable pages on trench diseases and trench life, not to mention the discussion of the effects of tropical diseases on war wounds and the special effect of aviation on otherwise simple wounds.

F. B. B.

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**THE ACTION OF MUSCLES, INCLUDING MUSCLE REST AND MUSCLE REEDUCATION.** By WILLIAM COLIN MACKENZIE, of the Staff of the Military Orthopedic Hospital, Shepherd's Bush, London. Pp. 267; 99 illustrations. New York: Paul B. Hoeber.

THIS is a book of interest alike to orthopedists, neurologists and anatomists. In it the muscles are treated from the viewpoints of physiological action, comparative anatomy and loss of function after nerve injury. All these are used in leading up to the consideration of physiological rest of muscles and reeducation. As the muscles constitute 45 per cent. of the total weight of the body, one can readily agree with the author that they are entitled to more scientific consideration than they usually receive. Since the muscles are dependent upon the nerves for their proper functioning, they may be regarded as the end-organs of nerves. In muscle paralysis after nerve injury the greatest care and attention is paid to the nerve, but usually the muscles are quite neglected. It is the author's purpose to try to bring out more prominently the needs of the muscles after nerve injury. To do this he first thoroughly examines into the action of certain muscles, or groups of muscles, having the same innervation. He does not try to cover all the muscles of the body, but selects those of greatest practical importance. Thus, under ulnar paralysis, he carefully goes into the function of the muscles innervated by the ulnar nerve. In this consideration of the

action of muscles he is quite complete and understandable, which is a contrast to some of the anatomies, where the action of muscles is stated often in a single sentence. From this careful analysis of the action of the various muscles involved he deduces the position of physiological rest for the arm and hand in ulnar nerve injury. Then, with the aid of photographs of patients, he explains his method of reëducation of these muscles, showing the sequence of joints to be exercised and the method of procedure. After the operation of suture for complete division of nerves the author considers that these movements should be tested for and encouraged, as soon as the surgical state of the wound is considered satisfactory. In a similar way he takes up the other important groups of muscles, and in each brings out many valuable points in treatment, based on the careful analysis of their normal physiology. W. H. F. A.

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THE ORGANS OF INTERNAL SECRETION. By IVO GEIKIE COBB, M.D., M.R.C.S. Pp. 274. New York: William Wood & Co., 1919.

As shifting as the eternal sands, goes on the shifting of our knowledge of endocrinology. Were each gland which has an internal secretion as its principal possession, to exhibit its structural pathology and its pathological physiology, in a manner independent of its fellows, how easy the subject would be! It is true that certain glands do exhibit certain clinical signs which focus the attention upon them, but with our ever broadening knowledge of endocrinology and hormonology what must one conjecture of the effect of this morbid change on other glands?

It is in a stage which, for want of a better term, we must name the "conjectural" that we seem to be anno domini MDCCCCXIX, and it is for this reason that the book under consideration leaves us unconvinced; not from the lack of ability of the author, but from the lack of evidence which writers on endocrinology have presented. Some of the cases, which Cobb describes, he has benefited by organ therapy without telling us on what deduction he based his treatment. Mixtures of extracts of many glands, well named according to modern ordnance terms, "mitrailleuse," by Leonard Williams, are used, but we search in vain for the reason and question, unanswered, "why"?

We commend the book, however, to those who wish to be brought up to date with endocrinology, for the literature has been well studied, sifted and assorted and we have as a result, a good compilation, containing perhaps, to those of venturesome disposition, many important suggestions. E. H. G.

AN INTRODUCTION TO THE MAMMALIAN DENTITION. By T. WINGATE TODD, Professor of Anatomy in the Western Reserve University, Cleveland, Ohio. Pp. 290; 100 illustrations. St. Louis: C. V. Mosby Company.

THIS is an interesting book on Mammalian teeth and skulls. If, as the preface seems to indicate, the author intends it for the dental undergraduate, he surely has a high opinion of the mental capacity of that individual. It would seem to be more adapted to an advanced college course in comparative anatomy, where specimens could be examined in detail by each member of the class. The author aims to follow out the evolution of tooth-forms from early mammalian and reptilian ancestors and to show how the various modern mammalian dentitions have been arrived at. In doing this he presents the American views regarding the evolution of tooth-forms and adopts the tritubercular theory of Cope and Osborn, in its most recent form, as his basis. In taking up the various mammalian orders in detail, he emphasizes the relationship between life habits and dentition. The illustrations are from photographs of actual jaws and skulls, and these, while giving the general aspect very well, sometimes fail to bring out the details necessary for a clear understanding of the text. These details might well have been shown by the insertion of little diagrams of the teeth at the side of the photographs.

W. H. F. A.

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ANNUAL REPORT OF THE DEPARTMENT OF PATHOLOGY OF THE JOHNS HOPKINS UNIVERSITY AND HOSPITAL. Fasciculus No. 2 of Vol. XVIII of the Johns Hopkins Reports, 1917. Pp. 342, with numerous figures. Baltimore: Johns Hopkins Press.

WE have here published under one cover accounts of the work conducted in the pathological department of the Johns Hopkins Medical School during 1917; all communications hitherto unpublished are presented in detail, as likewise articles which have appeared in various journals. Twenty-four papers are included, in addition to autopsy statistics and various reports; numerous excellent illustrations are given. A wide range of subjects are dealt with, including studies in gross pathology, pathological histology, immunity and metabolism, indicating the broad interests of this department. The individual papers are generally excellent and in accord with the well-established reputation of this department for thorough work and splendid reports.

J. A. K.

# PROGRESS OF MEDICAL SCIENCE

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## SURGERY

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UNDER THE CHARGE OF

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**Gunshot Affections of Large Joints.**—DAW (*British Jour. of Surg.*, October, 1918, vi, 191) says that gunshot injuries generally lead to very severe forms of obstruction to the normal movements of joints. Manipulation has its chief use in the correction of deformities, and in changing the position of a joint from one in which function is bad to one in which function is at its best if permanent stiffness is to be the final result. Improvement of mobility is more likely to be gained by slight movements followed by periods of rest or by slow stretching of contracted parts—in other words, by gradual change of position—rather than by forcible movements through a large range. Open operations to obtain mobility are rarely advantageous except in the case of the elbow-joint, where they are usually satisfactory. Massage and baths are valuable adjuvants to improve circulation and aid in the dispersal of scar tissue. Passive movements have a very limited value, and are often harmful. Active movements, especially those of normal use and occupation, are most valuable, and will often do more to increase mobility than any surgical means at our disposal.

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**Treatment of Ununited Gunshot Fractures.**—GROVES (*British Jour. of Surg.*, October, 1918, vi, 203) says that the introduction of a living autogenous bone graft is the main resource for the treatment of ununited fractures, and especially for those in which there has been a definite loss of substance. The existence of latent sepsis and the presence of extensive scars of skin, muscle and bone, however, make it much more difficult of success than when it is applied for the replacement of bone lost by disease, *e. g.*, a tumor or tuberculosis. The essential condition to be obtained in the graft bed is the removal of scar tissue, whether cutaneous, fibrous or osseous. Ragged bone end must be removed and no dependence placed upon them for osteogenesis or union. That a living autogenous graft continues to live when joined to living bone is

no longer a matter of theory or microscopic investigation. When it becomes fractured it produces callus just as does a living bone. That periosteum is not an essential element in the graft is proved by the fact that in many cases a naked bone graft heals in position and becomes united to its bed. The best example of this is in the living tibial peg driven into the neck of a fractured femur. Nevertheless the preservation of the periosteum is very desirable in all cases except those where the graft is entirely intramedullary. The role of the periosteum is remarkably demonstrated by the comparison of three types of operation: (1) Where the naked graft is used, increase in thickness of the graft, even after long survival, is very slow. Whenever sepsis supervenes, the graft becomes entirely exfoliated without depositing any new bone. (2) Where periosteal flaps with a thin layer of bone are turned down to bridge the gap, no new bone is deposited, and failure results. This shows that periosteum, even when retaining its attachment, will not deposit new bone in an adult. (3) Where a graft covered on one surface by its own periosteum is used, its behavior is different from either of the above groups. Increase in thickness occurs in all cases within a few months. In those cases in which secondary sepsis supervenes, there is an abundant deposit of new bone between the periosteum and the graft. The solid portion of the graft may be exfoliated, but a mass of new bone is left behind of larger bulk than that originally used. From these facts it may be inferred that the osteoblasts necessary for new bone formation are contained in the dense bone, but that the protecting and vascularizing matrix of the periosteum is necessary for their activity. The success of all plastic surgery depends largely upon accurate suturing. Bone being a tissue of slow growth and slow repair, requires more firm and lasting sutures than the soft tissues. There are three methods used for the fixation of a graft: (1) Suture by ordinary absorbable sutures; (2) fitting by accurate joinery; (3) fixation by means of metal screws, pins, wires, or plates. The series reported by Groves, contains 34 cases of autogenous bone grafting. Of these, 10 (29.4 per cent.) have been failures, 5 (14.7 per cent.) have been eventual successes in producing bone union after extrusion of the graft, and 19 (55.8 per cent.) have been complete successes.

**Changes in Growing Bone after Injury to Epiphyseal Cartilage Plate.**  
—HAAS (*Jour. Orthop. Surg.*, 1919, i, 67) says that the longitudinal growth of bone is maintained by changes taking place in the epiphyseal cartilage plate. As long as this highly differentiated cartilage mass persists there is opportunity for further increase in length, but with its ossification there is loss of that property. As a working principle it is necessary to know the exact portion of the epiphyseal cartilage plate that is most essential to bone growth. The greatest growth activity is localized in the cartilage columns of the epiphyseal cartilage plate and after the destruction of this portion of the plate, length growth practically terminates. The metaphyseal cartilage serves chiefly as a medium for or is the site where the newly formed cartilage is transformed into osseous tissue. For the proper functioning of the epiphyseal cartilage plate it is essential that it shall receive an adequate blood supply. If all the bloodvessels entering the bone in this region of the plate are destroyed, a very marked loss of growth takes place. This



loss of growth is much greater than when the nutrient artery is destroyed. Closely associated with the bloodvessels is the character of the constituents of the blood. If there is lacking some necessary chemical elements a loss of growth is likely to take place. Thus in certain diseases and in abnormalities of the endocrine system disturbances in growth frequently occur. Trauma is the most frequent cause of disturbances in growth of bones. It must be remembered that an injury in the region of the epiphyseal cartilage plate may be confined entirely to the superficial tissues, to the deeper tissues containing the vascular supply to the epiphyseal cartilage plate, to the epiphyseal cartilage plate itself or may be a combined injury of more than one of these structures. Upon the severity of the destructive process to these vital growing parts depends the resulting disturbances in growth.

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**Study of Buried Bone.**—COWAN and ELY (*Jour. Orthop. Surg.*, 1919, i, 101) made their study upon a series of knee-joint resections in the dog. A patella or the fragment of another bone, embedded fresh in the muscles of the animal from which it was removed, has a tendency to disappear, but does not disappear at least for a long time. In none of their cases had it disappeared completely. Its structure becomes less dense. The bone tissue itself may be replaced by fibrous tissue, especially at or near the circumference, or it may be absorbed. Absorption is the rule in the interior. Occasionally typical rarefying osteitis by osteoclasts is seen. More frequently the process seems to be one of simple absorption—"halisteresis." The method of absorption is often difficult to determine, for about many of the trabeculae there are no giant cells, no leukocytic infiltration, and no increased vascularity of the marrow. Many of the cells disappear early from the bone. Others stain well after the expiration of a long time. Death of bone is the rule. A patella, with a complete investment of bone and cartilage, does not resist absorption better than a bone fragment whose marrow is exposed to the surrounding tissue. A blood supply is established in the marrow of the buried bone. The marrow has a tendency to become fatty and fibrous, though lymphoid paths may persist. It is engorged in animals who have died with an acute infectious disease, as is the marrow of normal bone in such circumstances. In other words, it is functioning as marrow. Cartilage becomes eroded at its surface, and is replaced by fibrous tissue. Sometimes it disappears completely in areas. Its cells often stain well after a long time. Sometimes they die after a shorter time. The buttress underneath the cartilage almost always disappears early. Roughly, the changes in bone and cartilage are the same as those seen in atrophic, or proliferating arthritis.

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**Abduction Treatment of Fracture of the Neck of the Femur.**—WHITMAN (*Surg., Gynec. and Obst.*, 1918, xxvii, 578) says that non-union occurs in childhood under the same circumstances as in adult life, although there can be no question of the capacity of the tissues for repair. Repair after non-union is the rule when at open operation the fragments are freshened and adjusted, indicating that fixation in apposition is the first essential of success. Experience in bone grafting proves that union is possible under far less favorable conditions, as regards the blood supply, than in fracture of the neck of the femur. The obstacles

to repair, whether intrinsic or extrinsic, actual or fanciful, that have thus far justified inadequacy and neglect furnish the strongest presumptive evidence in favor of opportunity as the determining factor in the result. It has been already abundantly proved by practical experience that repair is possible in every variety of fracture at the hip and at any age, and although it cannot be asserted that opportunity will always assure success, it is self-evident that want of opportunity assures failure. Consequently, the responsibility for opportunity, upon which the result is primarily dependent, rests upon the one who selects and applies the treatment. This conclusion, however revolutionary as contrasted with conventional teaching, is, in effect, simply that surgical principles, whose application has been made practicable by the abduction method, should now govern the treatment of this as of other fractures.

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**Shall Operation for Hypertrophied Prostate be Done in Two Stages.—**

WRIGHT (*Surg., Gynec. and Obst.*, 1919, xxviii, 56) says that all cases, including those where only a small amount of residual urine is present, should be given several days of preliminary drainage before prostatectomy is done. Since cystotomy, which gives permanent drainage to the bladder and the pelvis of the kidneys, has been followed by death, the author believes it is better that drainage should be made by use of the catheter. Cystotomy should be reserved for use in those cases where catheterization, for any reason, is impossible; or, for use in those cases of acute cystitis that do not do well with permanent catheter. Since uremia has been known to follow the opening of a bladder which contained only 45 c.c. of residual urine, if compelled to do a cystotomy, it should only be performed after catheterization or aspiration of the bladder has been carried on for several days.

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**Carcinoma of the Stomach.**—DOUGLAS (*Surg., Gynec. and Obst.*, 1919, xxviii, 76) says that the conclusion reached by the pathologists of the Mayo Clinic where probably more material from excisions of ulcers and early carcinomata are examined with the greatest care than anywhere else in the world, should carry great conviction, even considering the work of Bullock. The considerable but not tabulated reports in cancer in a small area of the edge of an old ulcer, is proof positive that the change does occur, confirming the above statement. The evidence that cancer develops from chronic irritation and ulcers in other localities, adds probability that the same metamorphosis occurs in the stomach. The agreement of those who are opposed to the theory of carcinomatous degeneration in a large percentage of ulcers that a previous ulcer history may be obtained in from 5 to 17 per cent. together with the facts that diagnosis is not always certain, and that ulcers may perforate without previous symptoms, and that a long ulcer history is not contrary proof, would seem at least to make it a fair presumption that ulcer preceded cancer in a larger percentage of cases than their figures indicated. The results after gastro-enterostomy are the strongest presumptive evidence against carcinomatous degeneration of ulcers, but an explanation is not inconceivable, based on the rapid healing which usually occurs in ulcers near the pylorus after operation, and the theory of a possible inhibition of cancer formation after gastro-enterostomy, according to the theory of Gressot, on the possible digestion of

sloughing carcinoma, and remembering the claim that a large percentage of cancers originate in ulcers does not mean that a large percentage of ulcers necessarily become malignant. The following facts are not contested: (1) The mortality without operation is 100 per cent.; (2) the percentage of deaths from cancers of the stomach in the total death-rate is 1 per cent. (3) More than 30 per cent. of all cancers occur in the stomach. (4) Of late years the statistics at the large clinics show an operability of 38 (Mayo) to 39 (Bloodgood) per cent. of cases coming to the surgeon. Gastric ulcers are potentially cancer and a diagnosis macroscopically in the early stage of malignant development cannot be made; therefore, an old callous ulcer in a patient of the cancer age should, when possible, be excised. If small and not believed to be malignant, and only then, it may be destroyed by the cautery method, and a gastro-enterostomy done, or else a transgastric resection or pylorotomy performed whenever it seems even possible that carcinoma has begun at any point in the margin of the ulcer.

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## THERAPEUTICS

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UNDER THE CHARGE OF

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**Treatment of Influenza.**—From October 10 to December 9, 1918, there were admitted to a general hospital, B. E. F., France, 937 cases of influenza. Nearly all showed pulmonary symptoms and were serious in about one out of every four. The mortality was 2.77 per cent. SMALL and BLANCHARD (*British Med. Jour.*, March 1, 1919, 241) believe that this compares favorably with the death-rate in other places and therefore outline the treatment employed. The general management was that of a fever. As far as possible the patients were treated in the open air, a sufficiency of blankets, etc., being employed to ensure warmth. The diet consisted mainly of fluids—milk, beef tea, egg flips, etc.; beef tea they consider especially valuable because of its stimulating properties. The drinking of large quantities of fluid was encouraged for the promotion of elimination and the lessening of toxemia. The degree of debility produced was often extreme and was particularly associated with circulatory symptoms as well as marked general weakness. Absolute rest during the acute stage is of paramount importance. In the severer cases alarming symptoms followed any degree of movement. Sleep they consider of the utmost importance. The patients were given heroin, gr.  $\frac{1}{4}$  hypodermically, repeated once or twice, if tepid sponging proved insufficient to induce sleep. The patients were arranged in groups (unselected) of 15 and were put upon different drugs and the progress of the various groups noted and compared. Aconite, aspirin, sodium salicylate, belladonna, arsenic,

quinin, Dover's powder and gelsemium were tested in this way. None of them appeared to have the slightest influence, except belladonna (which showed evidence of beneficial action in a number of cases) and gelsemium. The patients treated by this drug improved in a manner far exceeding those given any other treatment. After a few doses they felt much better in every way. In most the temperature speedily commenced to fall and the improvement in the general condition was obvious. So great was the contrast that it was usually possible, without previous knowledge, to pick out the cases treated with this remedy. Beyond slight ocular disturbances in a very small number of cases they did not see any disadvantage in its use. When stimulants were indicated, alcohol (brandy, whisky or champagne) gave the best results, half an ounce every four hours or oftener if the case was urgent. Caffein, strychnin, adrenalin and pituitrin produced no beneficial results.

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**Fatigue in Irritable Heart and Other Conditions.**—Following Ryan's observation that general fatigue causes measurable shortening of the time interval between the appearance and fading of the white vasomotor reflex which is produced by stroking the skin with a blunt-edged instrument, KING (*Arch. Int. Med.*, 1919, xxiii, 527) made several hundred tests on soldiers suffering from "irritable heart" and other conditions. The "irritable heart" group are classified as physically inferior, constitutionally inferior, emotionally sensitive and neurotic, after Campbell; the smaller, organic group represents all patients with demonstrable cardiac lesions; a third group (post-infection) contains those patients developing symptoms of irritable heart after an acute infection, but in whom no organic disease of the heart can be demonstrated. After a review of the literature and a consideration of the nature of the phenomenon, King gives the following conclusions: (1) The quantitative estimation of fatigue by the white vasomotor reaction, as suggested by Ryan, is of value in the study of clinical conditions. Owing to the various sources of possible error in the test, it is more suitable for group study than for individual cases. (2) The day curve of fatigue estimations is much the same in the several groups of cases that have the syndrome of irritable heart as in those with organic heart disease. (3) Patients with irritable heart who fall into the groups of general constitutional inferiority or pure physical inferiority show very rapid fatigue on exercise. This fatigue can be measured and is an actual physical phenomenon and not of psychic origin. (4) There is a correspondence between the general body strength and the duration of the white vasomotor reflex. This suggests that there is a relationship between the strength of the skeletal musculature and the arteriolar musculature in a given individual. It is not considered, however, that the test is accurate enough to warrant estimating body strength from the vasomotor reflex in an individual case. (5) An unusual type of day fatigue curve, of V-shape, is usually found in patients convalescent from influenza. It is unlike the day curve obtained in any ambulant patient and may be characteristic of convalescence.

**OBSTETRICS**

UNDER THE CHARGE OF

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**Influenza Occurring in Pregnant Women.**—HARRIS (*Jour. Am. Med. Assn.*, April 5, 1919) has collected the statistics from 1350 cases of influenza complicating pregnancy. His results are tabulated and the conclusions are drawn from the examination of the tables. About half the pregnant women having eclampsia developed pneumonia, and of these 50 per cent. died, a gross mortality of 27 per cent. In those developing pneumonia the mortality was higher in the last three months of pregnancy. The largest number of cases occurred in the sixth, seventh and eighth months of gestation and the smallest number from the third to the fifth month. As regards the first two months of pregnancy, in many instances undoubtedly the existence of pregnancy was not suspected by the attending physician, and therefore these cases are not included in the reports. It seems too far to conclude that the pregnant woman is not more susceptible to the disease in any one month of pregnancy than in another. The disease was distinctly most fatal in the last three months of gestation. Sixty per cent. of the cases developing pneumonia in these months proved fatal. The mortality curve reached its highest point in the ninth month, with 61 per cent. When the gross mortality is reckoned the percentage is reduced somewhat, owing to the large number of cases reported for this period. In 626 cases uncomplicated by pneumonia, pregnancy was noted in 26 per cent., the ratio being somewhat higher in the first three months. This is not much in excess of the frequency of abortion one would expect under ordinary conditions. It must also be remembered that many of these abortions might have occurred in the absence of influenza or that this disease may have served only as a terminal factor in causing the expulsion of the ovum already abnormal. In cases complicated by pneumonia the interruption of pregnancy occurred in double frequency, being 52 per cent. in 585 cases. The first two months of pregnancy are disregarded, the percentage of pneumonia is still higher, the termination of pregnancy occurring in 62 per cent. of 308 cases. It is commonly believed that influenzal pneumonia almost always causes the interruption of gestation, but the surprising fact is that in 38 per cent. of the fatal cases the patients die without the interruption of pregnancy. This would indicate that when the ovum is normal and the placenta normally situated and developed the patient may pass through an extremely severe disturbance without causing the termination of pregnancy. In 743 patients in whom pregnancy was not interrupted mortality was 16 per cent. In 468 cases in which pregnancy was terminated mortality was 41 per cent. This ratio remains throughout the different stages of pregnancy during the first two months, but it has already been pointed out that regarding these two months it is difficult to draw definite conclusions. Unquestionably the interruption of pregnancy at any time makes th-

prognosis more grave. In cases complicated by pneumonia in 383 patients where pregnancy was not interrupted the mortality was 41 per cent. But the mortality was 63 per cent. in 395 patients where pregnancy terminated. It is possible from this data to construct an algebraic formula by which the mathematical probability of an interruption of pregnancy can be calculated. It may be concluded that the chances of the interruption of pregnancy are about doubled if the woman contracts both influenza and pneumonia over what they are if she has only influenza. Obstetricians usually believe that normally and without known complications abortion occurs once in five pregnancies. This ratio does not seem to be much altered by the presence of influenza alone. The mortality of influenza complicated by pneumonia in pregnant women is greatly increased by the interruption of pregnancy. The conclusions drawn from the study of these cases are that pneumonia complicated influenza in pregnant women in about half the cases. Of these patients 50 per cent. died. The mortality was greatest during the last three months. The gross mortality of all cases was 27 per cent. In cases without complication, pregnancy was interrupted in 26 per cent., and in those where influenza was complicated by pneumonia in 52 per cent. In the fatal cases of whatever sort, abortion or premature labor occurred in 62 per cent. Thus in 38 per cent. of the fatal cases the patient died without the interruption of pregnancy. When pregnant women suffered from influenza and had abortion or premature labor their mortality was 41 per cent., and when they escaped the interruption of pregnancy the mortality was 16 per cent.

**Influenza in the Newly Born Infant.**—ABT (*Jour. Am. Med. Assn.*, April 5, 1919) reports the case of a primipara who developed influenza. Labor developed in twenty-four hours after she was taken ill with influenza. The fetal heart sounds became rapid, but remained regular and indicated no disturbance of the fetal circulation during labor. When the amniotic liquid was discharged it was markedly stained with meconium. The child, a male, weighing six pounds twelve ounces, was spontaneously delivered. The infant's skin immediately after labor became grayish blue, and although the child cried strongly and the air passages seemed to clear this condition persisted. The child breathed promptly after birth and it seemed vigorous. Ten minutes after birth fine moist rales were heard in both lungs, but there was no dulness on percussion. On the following day the child was put to the breast and nursed well, but shortly afterward the breathing became rapid and labored. The respiration rose to 120. The temperature never exceeded 100°, falling to 97°. Cyanosis increased; respiration was superficial and rapid and the child occasionally uttered a weak cry. Examination of the baby's blood made on the day before its death showed a leukocytosis of 21,450, with a few of the nucleated red and some large pale white cells not classified. The polymorphonuclears were 58 per cent., the lymphocytes 35, large mononuclears 2.8 per cent., and eosinophiles none. During the third day of the infant's life finely crepitant rales appeared, particularly diffuse over both lungs. Cyanosis and dyspnea appeared and death occurred. At autopsy there were minute hemorrhages in the pericardium. The heart muscle was flabby, giving evidence of a parenchymatous myocarditis. On the heart valves there

was evidence of a beginning acute endocarditis involving especially the tricuspid valve. In both lungs there was confluent hemorrhagic bronchopneumonia. The spleen showed inflammation, with edema and passive hyperemia. In the kidneys there was no gross pathological change, and in the liver there was cloudy swelling. Cultures made from the organs of the child showed abundant colonies of streptococci. Over the lungs there were also a few colonies of *Staphylococcus aureus* and *albus* and many colonies of streptococci. Examination of the organs showed diffuse bronchopneumonia, streptococcus, septic nephritis, acute infection of the spleen, the streptococcus being the cause of the condition. The mother of the infant had a mild attack of influenza and recovered without complications. We must believe that the child was infected before birth.

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**Placental Tissue as a Galactagogue.**—CORNELL (*Surg., Gynec. and Obst.*, November, 1918) had the placenta of cows prepared by washing and drying and putting up in 5-grain capsules. These were given four times daily for twelve doses. The first dose was given as soon as the patient was able to take nourishment and had rest after labor. This generally occurred within twelve hours after delivery. There was no disturbance in digestion, and while a few patients objected to the odor of the preparation, aside from this there was no trouble. The placenta was used in more than 100 cases, but as the results were not satisfactory in the first cases only the last 100 cases have been selected. To compare methods of treatment, 70 other patients in the hospital at the same time and on the same floor and using the same food were investigated to observe their lactation. In the small ward containing three beds one or two of these patients would receive placental tissue while the other would not, but the patients were cared for by the same nurses. The results are tabulated, showing the age, nationality and general health of the patient, the method of delivery and the character of the puerperal period. It is concluded from this study that placental tissue has a favorable effect in the production of breast milk. The nationality, age and general condition of the mother and the sex of the infant have no influence on this result. Of those mothers who did not receive this preparation their infants began to gain on the fourth and fifth day after labor in 69 per cent. of the cases. Of those mothers who received this preparation their infants began to gain in weight on the fourth and fifth days after labor in 87 per cent. Of those mothers who did not take the placental extract, 24 per cent. of their children had regained their birth-rate before leaving the hospital, while of those who had taken the placental extract 44 per cent. regained their weight. The reviewer has recently tested dried placental extract in 3-grain doses, given three times daily after food, for several weeks. The results have been distinctly favorable, especially in women whose general nutrition was poor and when the general development of the woman was considerably below par.

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**Rotation of the Head by Forceps in Occipitoposterior Position.**—BILL (*Am. Jour. Obst.*, December, 1918) has rotated the head with forceps in 249 cases. In 170 the position was right occipitoposterior and in 79 left occipitoposterior. In 104 cases the head was at the pelvic brim.

its greatest diameter not having passed through. In 88 cases the head was in the pelvic cavity above the spines of the ischia and had not entirely passed through the os. In 43 the head was in the pelvic cavity and had entirely passed through the os and in 14 the head was at the pelvic outlet. Among these 14 cases were 11 in which the occiput had turned into the hull of the sacrum, the sagittal suture lying in the antero-posterior pelvic diameter. The forceps was applied to the sides of the head and the head rotated through the smaller arc of the circle. This varied from 100 to 180 degrees. There was no difficulty in any of these cases and the first essential was the accurate diagnosis of the exact position of the head so that the forceps could grasp it with an accurate application. If the instruments are turned in such a manner that the blades lie continually in the same axis any sort of good forceps may be used. Those with solid blades are preferable because they are more easily applied, the blades take up less room in the pelvis, the smoothness of the blades helps the rotation and they are more easily removed after the rotation is complete. The concavity of the pelvic curve with forceps should look toward the front, that is toward the child's face, in cases of posterior position. So far as the child's head is concerned this in reality gives a reverse application of the forceps. Complete flexion must be secured before the forceps blades are locked. The handles are then raised in the direction of the child's face and then carried around in a large circle, first toward the patient's thigh and then posteriorly. This tends to favor flexion of the head and a large sweeping movement of the handles tends to keep the blades of the forceps in the same axis throughout the rotation, thus allowing the head to turn without difficulty. Traction is not made until the head is in the normal anterior position, and if the rotation be properly carried out no force is required during the rotation. The handles of the forceps must not be twisted but must be carried through a large circle and traction must never be made while rotation is being accomplished. If the head is too firmly fixed in the pelvis its position may be altered slightly in order to effect rotation. The head should never be drawn down first before rotation is performed. After rotation is complete the forceps occupies a reverse position and the instrument must be removed and reapplied; but before removal it is well to make slight traction and fix the head in its new position and prevent a return to the old position. In very rare cases the head slips back before the reapplication is made and has outturned again. In making the reapplication the posterior blade should be first inserted and applied. After rotation there is usually very little difficulty in effecting delivery. While manual rotation has in some cases proved satisfactory, the forceps is better, as it gives more efficient control of the head. The operator must decide in each case as to the best time for carrying out each maneuver. The essentials of success in this method of treatment are the absolute diagnosis of the position and true cephalic application of the forceps, rotation without traction. The sweep of the handles of the forceps through the large circle, very slight traction to fix the head in its new position and the application of the posterior blade first and the second application of the forceps. This maneuver eliminates the necessity for excessive force in the delivery of abnormal cases and makes comparatively simple and easy the extraction of the head when it presents with the posterior position.



## GYNECOLOGY

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UNDER THE CHARGE OF

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**Cure of Prolapse in the Aged.**—The gynecologist is frequently troubled to know how to treat effectively the very old women who suffer from complete prolapsus of the vagina and uterus, especially when the vagina hangs down between the thighs, becoming thickened and often ulcerated. These patients are usually too old to stand a long operation and only an extensive operation will be effective since all the attachments of the uterus and vagina have been destroyed and the atrophic muscles of the perineum are so feeble that they give little chance of a perineal repair. In such cases MCARTHUR (*Med. Jour. Australia*, 1919, i, 149) suggests an operation that resembles a coat sleeve that has been sewed down the center and which therefore cannot be inverted. The operation is performed by stripping an area of mucous membrane from the anterior vaginal wall, about a finger breadth in width from just behind the orifice of the urethra to within 1 or 2 cm. of the junction of the cervix and vagina. A similar area is stripped from the posterior vaginal wall and then sewn together with a continuous catgut suture the anterior and posterior cut edges on the left side, followed by a similar suture on the right side, sewing three or four sutures on the left side, then a few sutures on the right side and thus alternating until both suture lines are complete. As the stitches are pulled taut, the cervix recedes into the vaginal orifice until it is lost to touch. The next procedure is to complete the perineorrhaphy by inserting three or four sutures into the already denuded perineum, tying them and completing the closure of the cut edges of the vaginal mucous membrane. When the operation is completed, there is practically a double vagina which prevents prolapse but at the same time allows the discharge of uterine secretions. The operation can be done very quickly and thus is especially serviceable in debilitated aged women.

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**Radium in Cancer.**—Skepticism in regard to the value of radium in the treatment of malignancy is rapidly disappearing on account of its extensive use and the brilliant results that have been achieved in many cases especially in epithelioma, fibroids and as a palliative measure in inoperable cancer. It is now generally agreed by the surgeons of the largest clinics that radium is a valuable adjunct in the treatment of malignancy. In some places it is used only as a palliative procedure while in other places it is also being used as an anti-operative treatment. In discussing this matter BOGGS (*New York Med. Jour.*, 1919, cix, 488) reminds us that several factors have brought radium into disrepute and have given the impression that the claims made were unjustified. Chief among these is allowing patients and the physicians who refer them to us to expect a permanent cure when only palliation and prolongation of

life is all that any one with ordinary medical intelligence could expect. The patient often cannot receive much palliation from any other method of treatment, but by the use of radium will improve rapidly for a time, or even a clinical cure will be obtained. Finally, on account of the extensive metastases, the patient will die after from six months to three years or more of prolongation of life. Then those who were watching the case or those who knew that radium had been used, will decide that radium had no value, without remembering or knowing the condition of the patient when radium was started. If one is to express an opinion as to the therapeutic value of a remedy, such statements should be guarded unless a study of all factors has been made and one should be without prejudice for or against the remedy. Many operators have used insufficient quantities of radium thus giving inefficient doses, or else, on the other hand, have overtreated the local growth, without attempting to treat the metastases. No one will deny that, under certain circumstances radium may be harmful rather than beneficial, since if the dose is too small or too long continued, stimulation rather than destruction may take place while, on the other hand, too large a dose may result in irreparable damage to normal tissues. Treatment of hopeless carcinoma in the past has been with morphin, but today, the author believes that it should be by radiotherapy since it is pitiful that patients with inoperable cancer, after their condition is pronounced hopeless, receive so little consideration. However, he cautions that thorough knowledge of the action of radium is essential because from that knowledge only may the proper dose be applied to produce the best results and haphazard use of radium should be discouraged. In estimating the value of radium therapy, its advocates do not claim that it supersedes surgery, but that it is a valuable adjunct to surgery, in helping to prevent recurrences after operation and in rendering inoperable cases operable and that it has proved itself one of the best palliatives we have in cases in which operation is impracticable and in many of such cases has brought about an apparent cure. In recurrent and inoperable carcinoma of the uterus, Boggs believes that radium might be considered the specific treatment, because it is the only method which retards the process to the same extent and gives the same amount of palliation. Radium is always less valuable in recurrent than in inoperable carcinoma of the uterus and since so much has been accomplished in the inoperable cases, in every primary case, no matter how early the operation has been performed, Boggs believes that there should be either ante- or postoperative treatment with radium, or both.

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**Operative Results in Myoma Uteri.**—There were 262 cases operated upon for uterine myomata at the Woman's Hospital in New York City during the year 1918, with a mortality of 4 patients, or 1.52 per cent., according to a report which has been published by BROWN (*Am. Jour. Obst.*, 1919, lxxix, 333), and 2 of these patients died of embolus. The remaining deaths were caused in one instance by intestinal obstruction occurring eight days after myomectomy associated with a ventral suspension and removal of tuberculous appendages, while the other death followed within three days after a supravaginal hysterectomy and removal of purulent appendages. The 2 deaths from embolus in

the present series of 260 cases taken in connection with 7 from a similar cause in the 1500 cases operated on during the eight years previous, in which there were 28 deaths from all causes, gives embolus as the largest causative factor in the fatal terminations. The next highest cause was peritonitis in 7 of the fatal cases. In accordance with the usual routine of the day, a follow-up investigation was conducted upon these patients, of whom, 117 patients reported for examination. Of this number, 99 were in excellent condition from a surgical standpoint, and stated that they felt absolutely well; 5 patients complained of menopausal symptoms, and their ages ranged from thirty-three to forty-two. In 3, both ovaries and tubes had been removed, and in the remaining 2, one ovary and tube had been saved. The few patients complaining of the forced menopause is striking, especially when one considers the 113 patients examined in whom there is no record of any symptoms except of a passing character which caused no inconvenience. It may be argued that these patients are hard-working women and not given to noting symptoms, which would be distressing to those of the more-leisure class, which no doubt, is true to a great extent. Nevertheless, Broun strongly believes that in the presence of tumor growth the function of the ovaries from the standpoint of internal secretions is greatly diminished and in this class of cases their importance in maintaining the nervous equilibrium of the patient is to a great extent overestimated. At any rate, this belief is apparently borne out by the study of these cases under consideration where usually one or both adnexa have been removed on account of circulatory changes or infection. Unless there is some special reason, such as a possible pregnancy, why should an ovary be conserved after its tube has been removed? The author thinks it better surgery to remove the ovary at the time the tube is excised and certainly in instances of the removal of the uterus and the remaining adnexa. This opinion founded on clinical experience is borne out by Sampson's studies of the tubal and ovarian circulation, since he has shown by his combined tubal and ovarian vascular injection specimens, that much care must be exercised in removal of the tube in order not to disturb the ovarian circulation and at times this disturbance is impossible to avoid on account of the abnormal distribution of the vessels. The results here reported by Broun represent the end-result of surgery applied to a series of consecutive cases by the full operating staff of the hospital and he doubts whether they can be equalled by roentgen rays or radium even in selected cases, especially when we consider the contra-indicating, unrecognizable degenerative changes present in such tumors and also the associated pathological conditions in the adnexa. Therefore, he would use radium or the roentgen rays in myomata for the purpose only of controlling bleeding and then only when the contents of the pelvis can be clearly mapped out. They are a valuable means under such conditions and by their use, what would otherwise be a mutilating operation, can be avoided.

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**Lacerations of the Vagina from Coitus.**—Coitus as the cause of a laceration of the vagina except in cases of rape or marked disproportion between the penis and vagina is quite rare and consequently it is interesting to note that one case of this kind has been reported by STOKES

(*Med. Jour. Australia*, 1919, i, 111) and two other cases have been reported by D'ARCY (*Med. Jour. Australia*, 1919, i, 172). All three of these patients had had children although in one of the cases, the ovaries had been removed several years ago and the vagina had undergone the characteristic atrophy subsequently. In a second case the vagina was somewhat shorter than normal due to an old perineal tear that had not been repaired but in the third case, the pelvic organs were absolutely normal and no explanation could be given for this unusual accident.

**Polypoid Adenoma of the Uterus.**—One of the very frequent forms which tumors of the uterus take is that of polypus and it is not unusual to hear this term used as though it constituted a diagnosis of a condition. It is plain, however, as emphasized by STRONG (*Am. Jour. Obst.*, 1919, lxxix, 502), that the word relates merely to external form and tells nothing of the structure and hence nothing of the nature of a tumor. There are a definite number of pathological conditions which may assume this form and these are generally not especially difficult of recognition in the gross specimen, so that it would be more satisfactory to speak of such tumors according to their specific class using the word "polypus" as a qualifying adjective, thus, "myoma polyposum," etc. What are perhaps most commonly meant when polypi of the uterus are spoken of are adenomata, either of the cervix or corpus uteri. These are tumors of common occurrence, but they have received rather scanty attention in text-books and reports, since their importance clinically has been considered to be slight. During the past five years there have occurred at the Woman's Hospital in New York City several cases where such polypoid adenomata have developed into malignancy of a type which appears to have striking individual characteristics. It should be noted that the polypoid form of these tumors is but a mechanical and secondary effect of the special region in which a tumor is produced and that it has no pathological significance in itself although it frequently does have a clinical significance which may be important, such as hemorrhage and necrosis, both due to interruptions in the blood supply. Pathologically, these tumors may be adenomata, myomata, carcinomata or sarcomata, or they may be an evidence of a simple polypoid hyperplasia of the uterine mucosa. Microscopically, the adenoma has in general all the characteristics that the hyperplasia has not, that is, the glands are irregular in size and outline, their cells show irregularities of arrangement and form and the relationships between gland and stroma are widely disturbed. The basal layer has the adenomatous changes as marked as the rest of the mucosa instead of the relatively simple glands of the normal basalis. According to Strong, there is no difficulty in recognizing an outspoken adenoma but the changes which separate it from simple hyperplasia are all relative and not absolute. The reason that uterine adenomata are polypoid is a physical one, namely, that they are surface tumors and represent non-invasive proliferations of simple glands, and the increase in bulk produced by the proliferation, being non-destructive of other tissue, tends to grow in the direction of least resistance, therefore, on a surface, the proliferation is outward.

## PATHOLOGY AND BACTERIOLOGY

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UNDER THE CHARGE OF

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**Determination of the Length of Life of Transfused Blood Corpuscles in Man.**—It is of interest and importance to know the relative length of life of red blood cells which have been transferred from one individual to another. Some attempts have been made to estimate this time, by injecting the corpuscles of widely different species into each other; or by transferring the nucleated corpuscles of birds into mammals with non-nucleated cells and observing the time of disappearance. These experiments introduce factors having no bearing upon the problem of homologous transfusion. ASHBY (*Jour. Exper. Med.*, 1919, xxix, 267) made use of the technic for grouping human erythrocytes into four groups. The corpuscles of group I are agglutinated by the serum of all other groups, but its serum has no agglutinating property. The sera of groups II and III agglutinate each other's corpuscles. Serum of group IV agglutinates all other corpuscles but group IV corpuscles are not agglutinated by any serum. It follows then that an individual in group I may receive the blood of any of the groups and that the blood of group IV may be given to any of the groups without danger. An individual having group IV blood may serve as a universal donor. When corpuscles of one group are transferred to any individual of another group, they may be recognized in the circulation by the difference in the agglutinating qualities. This fact was observed in test-tube mixtures of different bloods when it was found that the proportion of agglutinating cells was in relation to quantitative mixture of the two kinds of cells. The author found it possible to apply this to a study of cases after transfusion. After a recipient has been transfused with blood of a group other than his own, specimens of his blood treated with a serum that will agglutinate his own corpuscles, show unagglutinated corpuscles in large numbers. These agglutinated cells are the transfused corpuscles and their count is a quantitative index of the amount transfused. The life of the red cells was estimated at thirty days and over.

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**Observations on the Wassermann Reaction.**—LEWIS and NEWCOMER (*Jour. Exper. Med.*, 1919, xxix, 351) compared the use of the cholesterin antigen with the acetone insoluble antigen of Noguchi. In the experiments the antigens were applied in different tests. The Noguchi antigen was used according to the recently devised test in which use is made of the native human complement without the addition of guinea-pig serum. The cholesterol antigen was used in conjunction with the antishoop hemolytic system. It is, therefore, impossible to fully compare the results regarding the comparative value of the antigens. The results are nevertheless interesting in illustrating identical

results obtained by the two methods and from similar reactions obtained in the majority of the remaining cases. Nevertheless in a certain number of instances a four plus positive cholesterin reaction was obtained along with a negative Noguchi. In other instances exactly the reverse was found. The authors offer no interpretation for the latter result. In a number of cases without evidence of syphilis, but suffering from a variety of febrile diseases, various grades of positive reactions were obtained. The tests are not alone useful for the purpose of diagnosis but also in controlling treatment. The authors conclude "that the Wassermann reaction alone, by whatever method it may be done, can only be used in the diagnosis of syphilis in conjunction with the presumption based on other grounds. That it fails to appear in a considerable number of syphilitics is well known. That the reaction is positive in other conditions is not so generally recognized."

**Pathology of Epidemic Influenza.**—There has been considerable variation in opinion concerning the important lesions of epidemic influenza and the cause of death. The different interpretations which have been made upon the pathological findings at autopsy have led to a confusing nomenclature which has made it difficult for the clinician to correlate his clinical findings with the pathologist's reports. The terms bronchopneumonia, lobar, lobular, diffuse and interstitial pneumonia have left him "far at sea," and have given him little assistance in the study of subsequent cases. But the difficulties in the study of the pathology of influenza do not alone lie with the varying interpretations by different observers, but it has been amply demonstrated that in different regions the nature and distribution of the lesions varied quite considerably. There are two main factors which have led to the dogmatic deductions so largely at variance with each other: (1) It has been found that the bacterial agents associated with the B. *influenzæ* differ quite widely in different communities; in some regions the B. *influenzæ* was prevalent in fairly pure culture; in others it was associated with streptococci, staphylococci, pneumococci, M. *cattarrhalis* or B. *Friedländer*; grouping of these organisms seemed to have a material influence on the inflammatory process of the respiratory tract, as well as upon the constitutional manifestations. (2) The time of death, whether during the height of the acute epidemic or during the period following appeared to give results that are not entirely comparable. Where reports have been made upon autopsies carried out during the intensity of the epidemic a great similarity in the findings is obtained. Such findings differ, however, from the reports of cases dying late in the disease with their manifold complications. LYON (*Jour. Am. Med. Assn.*, 1919, lxxii, 924) reports upon 56 autopsies which were performed during the four weeks of the acute epidemic. The average duration of life after the onset was twelve days with the shortest of three days. Cyanosis was common about the head and face. Icterus was observed in six cases. The cases coming to autopsy during the first period of their acute illness showed as the outstanding lesion a hemorrhagic and serous pneumonia. This lesion was most conspicuous in the lower lobes but involved all lobes. There was always some air remaining within the involved tissue. The only reason why the entire five lobes of the lung were not uniformly involved was that death occurred before this was accomplished. Fol-

lowing this type of pneumonia and often present with it was a purulent pneumonia, lobular or patchy in distribution and sometimes even showing lobar characters. The lobar nature of this condition was the result of confluence of a number of lobular patches. The distribution of the lobular process was quite irregular and not confined to any lobe or portion of a lobe. Slight emphysema was not uncommon. Abscesses were not observed in his series. The bronchial lymph nodes were commonly enlarged and edematous. Pleurisy with effusion was common often being blood stained and still more frequently showing hemorrhagic lesions in the pleural walls. Only two cases showed empyema. The heart showed little change other than a mild grade of dilatation on the right side. The lesions of the spleen, liver and kidneys were not severe and usually of the type of granular degeneration. An interesting report to compare with this is that of MACCALLUM (*Jour. Am. Med. Assn.*, 1919, lxxii, 720) who differs quite frankly in his findings and conclusions. MacCallum reviews some of the bacteriology as observed in three different groups of cases. He is opposed to the consideration of the *B. influenzae* as the important agent in our recent epidemic. The causative agent he states is unknown, and it produces great lowering of resistance to bacterial invasion and is often followed by pneumonia caused by different types of pneumococci, staphylococcus aureus, streptococcus hemolyticus or the influenza bacillus. Thus in his consideration the pneumonia is a sequel or complication of influenza and is due to different organisms, depending upon regional distribution. From his findings he attempts to classify pneumonia according to the reactions induced by these different bacteria. Thus he speaks of a pneumococcal pneumonia, staphylococcal pneumonia, streptococcal pneumonia and pneumonia produced by *B. influenzae*. The pathological picture which he gives for the pneumococcal pneumonia is not the one which is familiarly known to us as lobar pneumonia and which occurring endemically and epidemically has long been recognized as a distinct pulmonary reaction with definite clinical and pathological characters. In fact his description of pneumococcal pneumonia corresponds more clearly with the pneumonia of epidemic influenza as described by Lyon. The epidemic disease, influenza, is viewed by MacCallum as comparable in many respects to measles and other acute exanthemata and is not necessarily a disease involving the respiratory tracts.

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**How the United States is Meeting the Tuberculosis War Problem.**—BUSCHNELL (*Am. Rev. of Tuberculosis*, 1918, ii, 387) gives an interesting summary of the work of the Government in meeting the problem of the tuberculous soldier. From the very beginning of the mobilization of troops steps were taken to examine all applicants for the earliest signs of tuberculosis. Methods of examination were necessarily different from those of civil life. The statements of the men could not be taken at their face value as some desired to conceal facts, while others, not desiring to enlist, might give a past history of infection when none had existed. Moreover, diagnosis must be upon positive marked signs and symptoms as the need of men was great and the examinations had to be rapid to avoid unnecessary delay and to prevent the entrance of claims for disabilities incurred in line of duty. From the total number of examinations made only 10,000 men were excluded from the National

Guard and the National Army. The majority of these cases were diagnosed within a month or two after entrance into service in which case, if the disease were of a chronic type, it is evident that the disability must be classed as not in line of duty and not entitling the soldier to a pension. As the tuberculous soldier costs the Government on an average of \$1000 for pensions, something over \$5,000,000 was saved by these exclusions. If the examinations had not been made 10,000 men at an average cost (according to Canada's estimate) of \$5000 would have been returned from Europe. For those who are returning and who developed active tuberculosis abroad the Government has provided hospitals in different parts of the United States with a total capacity (September, 1918) of 1305 beds. Physicians experienced in internal medicine and especially in tuberculosis are in great demand, as well as trained lay workers who will serve in teaching the returned soldier how to meet his new life. Because of the treatment prescribed for the tuberculous patient which means months of rest and quiet the problem is a very difficult one. The best results have been gained when the patients are treated far enough from family and friends that frequent visits home are impossible. A stern enforcement of the standardized course of treatment with a tact and kindly sympathy that will inspire the patient with the hope of recovery is expected to accomplish all that is desired in the reconstruction of the tuberculous soldier.

**Regulation of the Intestinal Flora of Dogs through Diet.**—TORREY (*Jour. Med. Res.*, 1919, xxxix, 415). The author used dogs for these studies because the intestinal flora more closely resembles that of human adults than does that of most other animals. Moreover dogs offer many advantages over rats, cats and monkeys. They eat a variety of food cleanly and quickly; the stools are generally moist, in ample amount and easily obtained; the flora seems more readily modified through diet probably due to the fact that the large intestine in dogs is relatively very short; they are more easily handled and less fastidious. Between four and five hundred fecal specimens were examined from some dozen dogs and the dietary effect determined of various sugars and starches, animal and vegetable proteins and fat on the number and types of bacteria in the intestinal content. Torrey used a number of special media and methods in estimating the variety of bacteria and their relative proportion. Stress is laid on the presence of *B. coli*, *B. acidophilus*, streptococcus, *B. bifidus*, anaërobic spore bearers,  $H_2S$  producing bacteria, the degree of putrefaction, gas production and the appearance of direct stained smears. The factors of weight in determining the growth and continuance of bacterial types in the intestinal tract are given as follows: (1) chemical character of the diet particularly the availability of the decomposition products for the metabolism of different bacterial types; (2) the completeness of the digestion and absorption of food within the small intestines; (3) the rapidity and degree to which the food residue is eliminated; (4) symbiosis and antagonism between bacterial groups. With man, factors (2) and (3) are of fundamental importance and dietary changes may not alter unfavorable bacterial conditions if these factors are at fault. Both of these factors act so vigorously in dogs that almost any type of fecal flora may be established by merely changing the diet. In a number of the experiments the animals were sacrificed and the bacterial flora



determined at various levels of the intestinal tract. A purely fermentative flora is simple in type and embraces only a few varieties of bacteria. In adults it is dominated by the *B. acidophilus*, and in breast-fed infants by *B. bifidus*. In a fermentative flora of a far more common type among adults, *B. coli* is predominant. A markedly putrefactive flora is complex and contains many varieties of bacteria. Either of two carbohydrates, lactose or dextrin, when added to a meat and rice diet develop a markedly fermentative flora, *B. acidophilus* dominating and almost completely suppressing the proteolytic types, even including *B. coli*. A diet of bread (dextrin) and milk (lactose) gave similar results. Saccharose, maltose and glucose gave changes much less marked; the former a moderate change toward a fermentative flora; the two latter little or no alteration. When unboiled milk was given, *B. coli* and streptococci predominated; while with boiled milk streptococci and *B. acidophilus*. Starchy foods, white bread, potatoes and beans, all tended to eliminate obligate putrefactive bacteria, rice was less effective. Proteins of mammalian tissue (beef hearts) markedly encouraged the growth and activity of the obligate putrefactive bacteria while a diet of fish did not do so. Milk casein showed far less tendency to give a putrefactive flora than did meat. Vegetable proteins did not offer the slightest encouragement to the growth of intestinal putrefactive types of bacteria. Fat had little or no effect, with large amounts there occurred an apparent reduction within certain groups. This paper is of special importance to all interested in bromatology; the experiments and methods are clearly described; the conclusions are logical and too broad interpretations are avoided.

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**Perfusion Experiments in the Study of Cellular Anaphylaxis.**—Two main theories have been offered regarding the mechanism of anaphylaxis. One group of observers claim that the phenomenon is dependent upon certain substances present in the circulating blood which act upon the antigen and convert it into toxic substances, while other individuals claim that the reaction is dependent upon the cellular activity of particular tissue which became sensitized to the antigen. The adherents to the cellular theory demonstrated the specific avidity of certain tissues after removal of the blood content by perfusion. LARSON and BELL (*Jour. Infect. Dis.*, 1919, xxvi, 185) studied the efficiency of the perfusion method in completely removing the blood from different organs. In carrying out perfusion with Locke's solution they particularly studied the liver and lungs of rabbits, and found that at the end of an hour the effluent still contained some blood and albumin. This was more prominently demonstrated if the experiment was interrupted and then the perfusion renewed. In such instances more albumin and blood appeared in the second effluent. They found, moreover, that if they colored the perfusing fluid with India ink, only particular regions of the liver and lung became stained by this solution. It appeared that in the ordinary perfusion method the easiest route was followed by the perfusing fluid and it did not necessarily travel all of the blood channels. Thus when the experiment was interrupted small quantities of the residual blood again made its appearance in the solution. The authors claim that the perfusion methods used in the experiments for demonstrating the cellular theory of anaphylaxis are insufficient to entirely remove the blood from the organs.

## HYGIENE AND PUBLIC HEALTH

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**Effective Malaria Control in a Rice-field District.**—GEIGER, PURDY and TARBETT (*Jour. Am. Med. Assn.*, March 22, 1919, No. 12, lxxii, pp. 844-847) state that malaria has been eliminated from a typical rice-field district. The question of the flight of *Anopheles quadrimaculatus* may of necessity be regarded from two angles, that of experiment and that of observation. In one, the largest experiment of its kind ever undertaken in the United States, the record flight was one mile. In the other observation there has been recorded continuously and on different occasions a flight of one and seven-tenths miles. The use of 10 grains of quinin sulphate by the mouth for sterilization of the blood of malaria carriers is evidently efficient for one malaria season if used actively over a period of thirty days. The completely negative clinical history of the nineteen malaria carriers discovered on microscopic examination indicates, on the one hand, an immense difficulty in obtaining complete malaria control, but emphasizes, on the other hand, the importance of the detection of human carriers.

**Persistence of the Virus of Poliomyelitis in the Nasopharynx.**—FLEXNER and AMOSS (*Jour. Exper. Med.*, April 1, 1919, pp. 379-395) state that the epidemiology of poliomyelitis has still to be worked out in detail, as many factors governing the spread of the disease remain to be discovered. That the virus or microbic cause is communicated by personal contact is now generally admitted. That the virus occurs in the nasopharynx, which constitutes the chief locus of ingress and egress to and from the body, is also conceded. The fact that the virus has been, if rarely, detected in healthy persons who have been in intimate contact with early cases of poliomyelitis, and even in certain individuals who have recovered from the acute effects of the disease, has led to the generalization that like some other diseases of bacterial origin, and notably epidemic meningitis, healthy and chronic carriers of the virus are frequent. This view has received its main support from Kling, Pettersson and Wenstedt, whose studies have been discussed. A critical analysis of the basis of their contention fails, however, to carry conviction, and the doubt which has arisen as to the true interpretation of their results is deepened by the more searching tests of Flexner and Amoss. The results of their experiments conform closely with clinical experience in the United States, at least, and especially with the observations made by epidemiologists in the course of the wide

epidemic in New York State and elsewhere during the summer and autumn of 1916. The conclusion reached at that time was to the effect that the communicability of the disease was a phenomenon chiefly of the early stages, while the frankly paralyzed person and the convalescent were to be feared much less. The authors state that in their experiments infection was secured with tissues obtained during the first week, approximately, of the disease, but not at later periods. The virus of poliomyelitis occurs in the nasopharynx of man and monkeys. In man it has been detected by the inoculation test in washings from acute cases, rarely in similar washings from healthy contacts, in the nasopharyngeal tissues obtained from fatal cases in the first week of infection, but rarely, if ever, from nasopharyngeal tissues removed surgically at later periods in the course of the disease. In monkeys, also, the virus has been detected in the secretions from acute experimental infections, in the nasopharyngeal tissues derived from early cases and rarely from cases several weeks or months after recovery from the acute symptoms. The inoculation of tonsils and adenoids obtained from cases of undoubted poliomyelitis either yielded definite results in the form of typical paralysis and histological lesions in the central nervous organs of the monkeys injected or no symptoms or lesions which could be confounded with poliomyelitis. The indefinite symptoms and atypical lesions described in a certain class of inoculated animals by Kling, Pettersson and Wernstedt were not encountered in the experiments of Flexner and Amoss. The deduction from the experiments reported is to the effect that the virus is regularly present in the nasopharynx in cases of poliomyelitis in the first days of illness, and especially in fatal cases; that it diminishes relatively quickly as the disease progresses, except in rare instances; and that it is unusual for a carrier state to be developed. Hence the period of greatest infectivity of patients would appear to be early in the disease, which is probably the time at which communication of the virus from person to person takes place. Available evidence proves that healthy carriers of the virus occur. The authors, however, possess data which indicate the frequency with which carriage arises. The fact that even after a severe and wide epidemic, such as occurred in the United States in 1916, the disease may virtually disappear within two or three years, points to the probability that enduring carriers of the active virus, whether healthy or chronic, are of exceptional occurrence.

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**The Role of the Hand in the Distribution of Influenza Virus and the Secondary Invaders.**—LYNCH and CUMMING (*Military Surgeon*, December, 1918) state that influenza, as well as the other so-called airborne or respiratory diseases, is essentially a hand-to-mouth infection. There are major and minor modes of transmission by indirect contact: by the former through tepid mess-kit wash-water and by the latter through intermediate objects, the hand being the conveyor in both instances. Among troops approximately 75 per cent. of the cases arise by the major route. This applies to troop transports as well as camps. Transmission by direct contact is only subsidiary to the indirect routes. The adoption of a universal method of washing mess-kits in boiling water will enormously reduce the prevalence of all mouth-borne infections. The prevention of the hand-to-mouth infections may

be accomplished by any measure which will prevent the unclean hand from visiting the mouth and nose and by the thorough cleansing of the hand after all such visits. The incubation period of influenza would appear to be two or three days. An epidemic of influenza among troops may be controlled by elimination of hand-contaminated dish water.

**The Effect of Heat, Age and Reaction on the Antiscorbutic Potency of Vegetables.**—HESS and UNGER (*Proc. Soc. of Exp. Biol. and Med.*, 1919, No. 4, xvi, p. 52) found that it required 35 gm. of the carrots used to feed laboratory animals to afford protection against scurvy to a guinea-pig. After the carrots had been cooked for three-quarters of an hour their addition to the dietary proved insufficient to protect. This was true even if the water in which they were boiled had been acidulated by the addition of 10 per cent. of vinegar, the only difference noted in the latter test being a less marked loss of weight. A parallel test was carried out with carrots which had been picked only a few days previous to the experiment. It was found that, even subsequent to cooking, 35 gm. of these carrots, when added to the dietary of hay, oats and water, were fully capable of protecting the animals. It is evident, therefore, that in a consideration of vegetables as a foodstuff we must take into account the factor of freshness. In dietetics this difference is intesified by the fact that older vegetables are tougher and therefore require and receive more prolonged cooking, thus further lessening their antiscorbutic value. The water in which the vegetables were cooked possessed little or none of the accessory factor, although 40 c.c. per capita were fed to the guinea-pigs; the animals did not, however, lose weight as rapidly as those receiving tap water. Five c.c. of canned tomatoes are sufficient to protect a guinea-pig from scurvy. If such tomatoes are boiled for five minutes their potency is slightly diminished, so that they should not be subjected to cooking when employed as an antiscorbutic for infants. Their efficacy was not diminished by rendering them slightly alkaline to phenolphthalein. Orange juice which had been made  $\frac{2}{3}$  alkaline to NaOH was found to be just as potent as in the acid state. The tomato as well as the orange juice was given by a pipette one-half to three-quarters of an hour following alkalization. Neither of these antiscorbutics, however, will retain their power long after they have been rendered alkaline. In judging of the effect of alkalization or of heat it is highly important to consider the length of time to which the antiscorbutic has been subjected to this influence.

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All communications should be addressed to—

DR. GEORGE MORRIS PIERSON, 1913 Spruce St., Philadelphia, Pa., U. S. A.

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